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Stress-related depression: neuroendocrine, genetic, and therapeutical aspects

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Abbrevations and acronyms

3,5-THP	3α,5α-Tetrahydroprogesterone
5-HTTLPR	Serotonin-transporter-linked polymorphic region
ABCB1	ATP-binding cassette B1
ACTH	Adrenocorticotrope hormone
AVP	Arginine vasopressin
BDNF	Brain derived neurotrophic factor
CRH	Corticotropin-releasing hormone
CRHBP	Corticotropin-releasing hormone-binding protein
CRHR	CRH receptor (CRHR1 and CRHR2)
Dex/CRH-test	Dexamethasone/CRH-test
DNA	Desoxyribonucleic acid
FKBP5	FK506 binding proteine
G x E	Gene environment interaction
GABA	Gamma-aminobutyric acid
GHB	Gamma-hydroxybutyrate
GR	Glucocorticoid receptor
GRIK4	Kainic-acid-type glutamate receptor KA1
GWAS	Genome-wide association study
HPA axis	Hypothalamic-pituitary-adrenal axis
HTR2A	5-Hydroxytryptamine receptor 2A
MAO-I	Monoamine oxidase inhibitor
MARS	Munich Antidepressant Response Signature project
Met	Methionine
MR	Mineralocorticoid receptor
OXT	Oxytocin
PN	Paraventricular nucleus
PCLO	Protein piccolo
P-GP	P-glycoprotein
POMC	Proopiomelanocortin
SANS	Sympathetic autonomic nervous system
SN	Supraoptic nucleus
SNP	Single nucleotid polymorphism
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor

STAR*D	Sequenced Treatment Alternatives to Relieve Depression
Val	Valine

Abstract

Objective: To summarize current concepts on neuroendocrine and genetic principles underlying stress-related depression and to discuss the challenges of personalized treatment in depression.

Methods: Review of the literature pertaining to genetic and neuroendocrine basis of stress-related depression including aspects of treatment response with a focus on the hypothalamus-pituitary-adrenal (HPA) axis.

Results: There is increasing evidence that genetic polymorphisms and dysregulation of the HPA axis are associated with the pathophysiology of stress-related depression. Individual stress hormone reactivity seems to be determined by a combination of genetic and environmental factors, contributing to both, resilience or vulnerability.

Conclusions: Although substantial progress has been made, current knowledge is still limited. Further basic and clinical research is needed to identify specific subgroups and to minimize heterogeneity of the depression phenotype. A better characterization is essential to detect genetic and functional predictors of antidepressant treatment response to follow the vision of personalized therapy in psychiatry.

5 keywords: stress, depression, neuroendocrinology, genetics, antidepressant response

Introduction

Stress is a complex reaction, which serves the maintenance of homeostasis under hazardous conditions. The most important functional stress systems are the sympathic autonomous nervous system (SANS) and the hypothalamus-pituitary-adrenal (HPA) axis. The classical stress hormones are corticotropin-releasing hormone (CRH), arginine-vasopressin (AVP), adrenocorticotropic hormone (ACTH), and cortisol. Apart from peripheral effects, they act as central neuromodulators and influence higher mental activities such as emotions, cognition and behavior. Since dysregulations of the HPA axis and alterations in CRH activity are relevant to the pathogenesis of depression, we focus on these systems in the present review. At the same time, genetic alterations determine individual patterns of the stress reaction, vulnerability to stress-related disorders, and antidepressant treatment response. Recently, several attempts have been made to directly target the HPA and CRH system to optimize antidepressant treatment.

Stress axis and stress hormones

In a situation of psychological stress, an activation of limbic pathways (mainly amygdala and hippocampus [HC]) induces the secretion of CRH and AVP from the paraventricular (PN) and supraoptic (SN) nuclei of the hypothalamus. Both peptides access the anterior pituitary gland either through blood vessels (CRH) or neurons (AVP), where they induce the release of ACTH. ACTH acts at the adrenal glands and stimulates the synthesis and secretion of cortisol via specific ACTH receptors. Cortisol initiates a variety of reactions, with the most important effects being on endocrinological, immunological, and mental functioning. The stress response is terminated via a negative feed-back mechanism. Cortisol stimulates central glucocorticoid receptors (GR) leading to an inhibition of CRH and AVP release (see Figure 1, left side).

- Figure 1 about here -

CRH is the central regulator of the HPA axis and is regarded as the main stress hormone in the brain (Holsboer and Ising 2010). It acts as a neuromodulator and can be found in neuronal pathways in a number of brain regions, with the highest concentrations in the hypothalamus, the amygdala, cerebrocortical areas and septum (Boorse and Denver 2006; Gallagher et al. 2008). CRH directly activates both of the physiological stress systems, the noradrenergic SANS and the steroidal HPA axis (Tsatsanis et al. 2007). Three related CRH ligands, urocortin 1-3, and two receptors, CRHR1 and CRHR2, could be identified to date (Hauger et al. 2003). Urocortin 1 has a high affinity to CRHR1, while urocortins 1-3 but not CRH have a high affinity to CRHR2 (Fekete and Zorrilla 2007; Vaughan et al. 1995). CRHR1 receptor stimulation by CRH is the central mechanism for HPA axis activation (Binder and Nemeroff 2010), while animal studies suggested a stress response terminating effect of urocortin-mediated CRHR2 stimulation (Neufeld-Cohen et al. 2010; Tanaka and Telegdy 2008). The fact that urocortin-deficiency induces anxiety-type behaviors suggests that urocortin is acting through CRHR2 to maintain a basal low anxiety behavior. As suggested previously, it is tempting to speculate that urocortin plays a role in anxiety-type behaviors induced by stressful stimuli through the activation of CRHR1 in discrete brain regions (Gysling et al., 2004). The CRH-binding protein (CRHBP) regulates the biological activity of CRH and thus is suggested to be a key modulator of the neuronal CRH activity (Behan et al. 1993). AVP is a peptide hormone with central neuromodulatory effects, which - synergistically with CRH - activates the HPA axis, but with less impact on the acute stress response than CRH (von Bardeleben et al. 1985). However, during chronic expose to stress, hypothalamic CRH secretion declines in favor of a pronounced increase of AVP mRNA and peptide concentrations (Chowdrey et al. 1995; Ma et al. 1997; Ma and Lightman 1998). In addition, animals with pronounced anxiety-related behaviors show HPA hyperactivity and an overexpression of central AVP, which both

may be reversed under treatment with antidepressant drugs (Keck et al. 2003b; Landgraf 2006).

The target function of the HPA axis is the release of cortisol from the adrenal gland. Cortisol triggers those physiological functions, which are central for the adaptation of the organism facing danger. It may produce anxiety, agitation and dysphoria in humans, but also opposite effects, such as anxiolytic and euphoric effects, and even a transient enhancement of memory functions have been described (de Quervain et al. 2011; Soravia et al. 2006). Some of the corticoid effects are due to a direct activation of genes (Sato et al. 2008), however, most effects of cortisol are mediated by two intracellular receptors: the GR and the mineralocorticoid (MR) receptor. MRs have a high affinity, GRs have a low affinity to cortisol. The highest density of both receptors in the brain is found in the HC. A normalization of HPA axis overactivity following ceasing of threatening stimuli is mostly due to GR activation by high plasma levels of cortisol. GR activation leads to a rapid decrease of CRH, AVP and ACTH secretion. This negative feedback mechanism guarantees an adequate adaptation to the environment. A well-established method to detect dysregulations of the HPA axis is the combined dexamethasone/CRH test (Dex/CRH-test) (Heuser et al. 1994; Holsboer et al. 1987; von Bardeleben and Holsboer 1988). For details of the procedure see Figure 2.

- Figure 2 about here -

Stress and depression

The two main hypotheses of the relation of stress and depression comprise a central CRH/CRHR1 hyperactivity (Holsboer and Ising 2010) and an MR/GR dysbalance (de Kloet et al. 2007).

Following CRH-initiated HPA activation, the determining factor for an adequate termination is the integrity of the GR-mediated negative feedback mechanism. GR desensitization may lead to persisting hypercortisolemia and elevated concentrations of CRH, AVP and ACTH (Feder et al. 2009). According to the MR/GR dysbalance hypothesis of depression, MRs have a preventive influence on the stress response, while GRs terminate it and mediate the recovery from stress. Thus - acquired or inherited - dysbalances in the expression or sensitivity of these receptors might be the cause of either an inadequate initiation and/or termination of the stress response, leading to a higher vulnerability for stress-related psychopathology. Moreover, a correction of such dysbalance might be a key mechanism in the treatment of these disorders (de Kloet et al. 2007).

The Dex/CRH-test is a validated and established method to detect dysregulations of the HPA axis in depression (Heuser et al. 1994). HPA hyperactivity can be measured in most acute depressive episodes, and normalization of neuroendocrine function correlate with treatment response (Ising et al. 2005). Impaired corticosteroid signaling and overactivity of CRH seems to be crucial in the pathophysiology of depression (Figure 1, right side). Moreover, a reduction of HPA hyperactivity after two weeks of antidepressant treatment predicts a remission during the course of the therapy. This effect constitutes the role of the Dex/CRH-test as a potential biomarker of depression (Ising et al. 2007).

Genetic underpinnings of stress and depression

The development of stress-related disorders is explained by the three-hit hypothesis: genetic variations (first hit) interact with childhood experiences (second hit) and determine cerebral or other physical and psychological maladaptations to later challenging experiences (third hit) (de Kloet et al. 2007; Elder and Mosack 2011). According to de Kloet et al. (2007), the main physiological issue of this hypothesis is the shift of the role of cortisol from protection to adversity. Here, the aforementioned MR/GR dysbalance gains relevance, as it might be the

key dysfunction that leads to a higher vulnerability towards childhood or adult trauma, thus resulting in the manifestation of stress-related psychiatric disorders. As the HPA axis has a biological key function for adaptation to stress, genetic variations of its components are of special interest. The most common targets for studying genetic variations are single nucleotide polymorphisms (SNPs). SNPs are mutations of particular base pairs in desoxyribonucleic acid (DNA) sequences, with an incidence of at least 1% (Müller-Myhsok 2005). SNPs have various effects on gene expression, such as direct changes in amino acid expression, indirect alterations of promoter activity, transcription efficacy, splicing, messenger ribonucleic acid stability and translation efficacy (Kimchi-Sarfaty et al. 2007). Often, SNPs appear in combinations (haplotypes), and different haplotypes may exist in the same gene. Thereby, variations of SNPs exert their effects on complex physiological mechanisms, and it is hypothesized that SNPs also modulate higher cognitive and behavioral functions. A common method for studying the relationship between genes and depression is the search of polymorphisms in candidate genes, which appear more often in patients with a depressive disorder compared to healthy subjects. On the basis of known pathophysiological mechanisms of depression, respective genes are identified and examined.

Serotonin

As the serotonergic system plays a key role in the neurobiology of depression, early genetic studies focused on elements of serotonin neurotransmission and polymorphisms in the serotonin-transporter-linked polymorphic region (5-HTTLPR) gene gained special attention in this regard. In the 1990's, first studies were published which linked 5-HTTLPR polymorphisms to psychopathology, especially to anxiety traits (Lesch et al. 1996). Up to now, 40 variants of the serotonin receptor genes have been studied (Illi et al. 2009). Although subsequent studies showed mixed results (Anguelova et al. 2003; Clarke et al. 2010; Munafo et al. 2009b; Schinka et al. 2004; Wankerl et al. 2010; Willis-Owen et al. 2005), a recent meta-

analysis including 54 studies found a strong effect of the s-allele of the 5-HTTLPR on the development of stress and depression (Karg et al. 2011) also pointing to the necessity of differentiation of distinct types of stress (e.g. due to childhood maltreatment or medical illness).

Brain derived neurotrophic factor (BDNF)

BDNF is crucial for hippocampal plasticity and patients with depression appear to have reduced hippocampal volumes, possibly due to glucocorticoid induced impairment of BDNF expression (Kaymak et al. 2010; Malykhin et al. 2010; Nifosi et al. 2010). Carriers of the met-allele of the val66met polymorphism of the BDNF gene showed an increased HPA activity (Schüle et al. 2006) and more pronounced depressive symptoms (Groves 2007). There also appears to be a gene x environment (G x E) interaction background of depression for this SNP and early childhood trauma (Lavebratt et al. 2010), while the val/val-genotype may have a neuroprotective role in older patients (Kanellopoulos et al. 2011). However, a recent study demonstrated an association between the BDNF val/val-genotype and major depression (Suchanek et al. 2011). In addition, the BDNF polymorphism G-712A has been associated with depression (Sun et al. 2011).

Corticoid receptors and CRH

Because of the strong interdependency of stress, HPA regulation, and depression, genes of the CRH system and the HPA axis are of special interest for genetic studies. The best evaluated and most important genes with an impact on HPA activity are those that encode for the MR and GR. Two MR (-2 G/C and I180V) and six GR (TthIIII, ER22/23EK, N363S, BclI site and A3669G) variants exerting such influences are known. Moreover, MR-I180V was associated with depressive psychopathology (DeRijk et al. 2011). Polymorphisms of the CRHR2 gene were associated both positively as well as negatively with affective disorders (Binder and

Nemeroff 2010), which puts into question its role in regulating the stress response in the brain . The findings are more consistent for the CRHR1 polymorphisms. Interactions of CRHR1 polymorphisms with traumatic life events on the development of neuroticism (Deyoung et al. 2011) and the incidence of suicide intents (Wasserman et al. 2008) could be identified. One of these polymorphisms (T-allele of rs4792887) was part of a 3 SNP haplotype which interacted with childhood abuse, and was predictive for the severity of depressive episodes in adult life (Bradley et al. 2008). In contrast, carriers of the less frequent C-allele of this polymorphism who experienced childhood abuse showed much less depressive symptoms in adult life. This protective effect was most pronounced for the three SNP haplotypes TCA (rs7209436, rs4792887 and rs110402) and TAT (rs7209436, rs110402 and rs242924). The precise biological effects of these haplotypes are unknown, but these results indicate a relationship between genetic variations in the stress hormone system, early life trauma and the development of adult depression (Bradley et al. 2008). A recent study confirmed the effect of an interaction of CRHR1 gene variants and childhood maltreatment on the development of depression (Grabe et al. 2010). Apart from the CRH system, SNPs in genes coding for the vasopressin V1B receptor and the angiotensin-converting enzyme showed effects on Dex/CRH reactivity and on the vulnerability for stress-related depression (Baghai et al. 2006; van West et al. 2004).

FK506 binding protein

Other important candidates for the development of stress-related depression are variants of the co-chaperone FK506 binding protein (FKBP5) (Binder 2009; DeRijk and de Kloet 2008). FKBP5 is able to bind to the GR and thus to regulate its sensitivity: cortisols affinity towards the receptor and the efficiency of the receptors nuclear translocation are reduced. In a study including 457 patients with depression and 2286 healthy controls, an association of a polymorphism in the FKBP5 gene (rs1360780) and depressive disorder could be shown

(Lavebratt et al. 2010). A recent study could demonstrate an association between a variation in the FKBP5 gene (rs9470080) and both cortisol secretion, and symptoms of depression (Velders et al. 2011).

Genome-wide association studies (GWAS)

A powerful tool for studying the genetic determinants of diseases are GWAS. However, to date the results of these analyses concerning affective disorders are quite sobering. A GWAS of 435 291 SNPs from DNA of 1738 depressive patients and 1802 controls did not show any significant SNP-phenotype association. A possible relevance of two SNPs in the protein piccolo (PCLO) gene (rs2715148 and rs2522833, affecting monoaminergic neurotransmission) was demonstrated. Despite the theoretical appeal of this finding, no association of PCLO and depression could be shown in a replication sample of the same study (Sullivan et al. 2009). Two additional GWAS including DNA analyses of 1514 depressive patients and 2052 controls and a meta-analysis of about half a million SNPs with suspected relevance for depression also did not show any significant associations (Muglia et al. 2010). A systematic review of 57 previously reported candidate genes, of which 92 SNPs were mapped using data from the Genetic Association Information Network GWAS in major depressive disorder, found poor replication of candidate genes, possibly pointing to publication bias and false-positive findings in previous candidate gene studies (Bosker et al. 2011). However, three genome-wide association studies published recently could identify candidate genes for major depression: GRM7, a glutamate metabotropic receptor gene (Shyn et al. 2011), RORA (rs12912233), a gene important for circadian rhythms (Terracciano et al. 2011), and SLC6A15 (rs1545843 and rs1031681), a neuron-specific neutral amino acid transporter gene (Kohli et al. 2011). Replication studies are needed to evaluate the relevance of these findings for the genetic underpinnings of stress-related depression.

Because earlier results of GWAS were dissatisfying, it was a consequent step to include environmental and developmental factors to the genetic studies. G x E interactions are closer to the aforementioned three hit hypothesis of depression, as they go beyond monocausal explanations. By these means, it could be demonstrated that hetero- and homozygote s-allele carriers of the 5-HTTLPR gene suffer more from critical life events than l-allele carriers. This polymorphism is associated with increased long-term negative effects of traumatic experiences on adult depression symptoms (Caspi et al. 2003; Uher et al. 2011). Although this is an important finding, other studies could not replicate these results (Munafo et al. 2009a). A gene x gene x environment (G x G x E) interaction between a CRHR1- and a 5-HTTLPR polymorphism with childhood trauma was able to predict adult depressive episodes (Ressler et al. 2010). Other interactions could be found for BDNF- and 5-HTTLPR variants with childhood trauma and social support. Abused children, who were s-allele carriers of 5-HTTLPR had fewer symptoms of depression, by having received social support. This shows an environment-dependent development of genetic risk factors, which is a strong argument for psychosocial interventions especially in cases with a positive history of childhood trauma (Kaufman et al. 2004). Moreover, abused children who were homozygote met/met-allele carriers of the BDNF gene and homozygote for the s-allele of 5-HTTLPR had the highest frequency of depression (Kaufman et al. 2006). A recent study confirmed the importance of BDNF gene and childhood trauma interactions for adult depression (Juhasz et al. 2011). One of the most intriguing findings in G x E research was an interaction of childhood maltreatment with a SNP of the FKBP5 gene (TT genotype of rs1360780) on the intensity of depressive symptoms in a sample of 2157 subjects (Appel et al. 2011). This is of special interest, as the gene product of FKBP5 directly affects GR sensitivity, and thus the potential susceptibility to stress-related disorders. The authors concluded that the large effect sizes would warrant the use of rs1360780 in prediction models for depression in individuals that have suffered from childhood maltreatment. It is evident that the gene-phenotype associations regarding affective

disorders are of an extraordinary complexity taking into account that genetic alterations such as copy number variations or even non-coding DNA sequences might also be relevant for the development of depression (Glessner et al. 2010). In future, whole-genome deep sequencing techniques may provide new insights into the effects of rare genetic variations in psychiatric disorders (Rudan 2010).

A novel approach to investigate the interactions of genes and environment is the analysis of epigenetic mechanisms. These are processes, by which quantity, location, and time of gene expression are altered by chemical modulation of DNA transcription. The most common epigenetic mechanisms are methylation of promoter cytosines and modification of histone proteins by either acetylation, methylation, or phosphorylation (Mill and Petronis 2007; Schroeder et al. 2010). Thus, environmental factors can directly act on the activation or deactivation of genes. In rats, maternal behavior had effects on the expression of GR and hence on stress reactivity. Regulation of GR expression was altered by histone acetylation and the promoter methylation (Fish et al. 2004; Weaver et al. 2004). Later, these findings could be translated into humans. Postmortem HC from suicide victims with and without history of childhood maltreatment and controls was examined for epigenetic differences in a neuron-specific GR (NR3C1) promoter (McGowan et al. 2009). NR3C1 gene expression was decreased in HC from suicide victims with history of maltreatment, compared to the other conditions. This study could show that early life adversities may cause lasting changes in cerebral GR expression and thus in the regulation of the stress response. In a recent study, McGowan et al. (2011) were able to identify a non-random pattern of epigenetic changes across broad genomic areas in HC of adult rats, in response to natural variations of maternal care. It could be shown, that epigenetic modifications are not limited to single candidate gene promoters, but also involve transcriptional and intragenic sequences among others. These results illustrate the crucial role of early life experiences for the development of physiological

adaptation mechanisms, such as the HPA axis regulation, and thus the reactivity towards stressors in the adult life. Interestingly, some of the epigenetic changes can pharmacologically be reversed with the histone deacetylase inhibitor trichostatin A and the methyl donor L-methionine, opening a broad field of potentially therapeutic interventions (Weaver et al. 2005; 2006). Epigenetic research, together with other non-genetic approaches such as proteomics, metabolomics and connectomics (i.e., the mapping of neuronal connections in the brain by combining neuroimaging and histological data), is in its beginnings, but is regarded as a major future direction of investigating the complex interactions of physiological and environmental factors on the development of stress-related disorders (Dudley et al. 2011).

Antidepressant response: hormones and genes

Several studies have reported that only about half of the patients respond to a first antidepressant therapy, and up to two thirds of all patients do not achieve complete remission (Kupfer 2005; Nierenberg et al. 2011; Rush et al. 2006). The *Munich Antidepressant Response Signature* (MARS) project serves the investigation of neuroendocrine and genetic determinants of antidepressant treatment response. Using a naturalistic longitudinal design, data of about 900 depressive inpatients have been gathered for SNP analyses and assessment of psychopathology. Dex/CRH-tests have been measured in about one-third of these patients. The most important predictor for remission was an improvement of symptoms within the first two weeks of treatment which was accompanied by a normalization of HPA-activity (Hennings et al. 2009). Moreover, the Dex/CRH-test may be of predictive value as earlier studies have shown that a normalization of HPA activity preceded a favourable response to antidepressant treatment (Ising et al. 2007; Schüle 2007).

Recent genetic studies give examples of how, to a certain extent, antidepressant treatment response is associated with polymorphisms of genes which code for elements of the HPA axis (Binder 2009; Binder and Holsboer 2006; Binder et al. 2009; Binder and Nemeroff 2010;

Claes 2009; Drago et al. 2009). Four genes of the HPA system seem to be of significance: the CRHBP gene (Binder et al. 2010), a 3 SNP-haplotype in the CRHR1 gene (Licinio et al. 2004; Liu et al. 2007), a variant of the FKBP5 gene (Binder et al. 2004), and a functional polymorphism in the GR gene (ER22/23EK) (van Rossum et al. 2006).

SNPs of 10 genes with associations to the CRH and AVP regulation were studied in the *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) sample in 1768 depressive outpatients. Carriers of the T-allele of a SNP in the CRHBP gene (rs10473984) with Hispanic or Afroamerican heritage, showed a worse response to citalopram treatment. This was paralleled by higher levels of plasma ACTH (Binder et al. 2010). Associations of a 3 SNP-haplotype in the CRHR1 gene with an improved response to fluoxetine and desipramine could be demonstrated in a Hispanic and Chinese population (Liebsch et al. 1999; Liu et al. 2007). Several studies investigated the association of polymorphisms in the FKBP5 gene and response to antidepressant treatment, with partly conflicting results (Binder et al. 2004; Kirchheiner et al. 2008; Lekman et al. 2008; Papiol et al. 2007; Perroud et al. 2011; Sarginson et al. 2010; Tsai et al. 2007). A meta-analysis of eight studies showed a significant association between the A-allele of the FKBP5 polymorphism rs4713916 and an improved response to antidepressant treatment, but not for the other tested variants (Zou et al. 2010).

In the MARS as well as in the STAR*D sample, polymorphisms of the FKBP5 gene showed interactions with the kainic-acid-type glutamate receptor KA1 (GRIK4) gene and the 5HT2A receptor gene on the treatment response to antidepressant treatment. A 3 SNP model (FKBP5 rs1360780, GRIK4 rs12800734, HTR2A rs17288723) could explain 13.1 % of the remission variance after five weeks of treatment (Horstmann et al. 2010). In both samples, associations of SNPs of the 5HT2A receptor gene with the antidepressant treatment response could be shown, but not for the same polymorphisms (Lucae et al. 2010).

Other studies focused on genes which determine the availability of antidepressants in the brain, i.e. genes coding for hepatic cytochrome P450 enzymes and transport proteins of the blood-brain barrier such as the ATP-binding cassette B1 (ABCB1) gene expressing the P-glycoprotein (P-GP). P-GP is part of the blood-brain barrier and essential for the active back transport of its substrates into the blood. Polymorphisms in the ABCB1 gene were associated with treatment response in patients who were treated with substrates of ABCB1/P-GP (Uhr et al. 2008). However, another study failed to show an effect of ABCB1 polymorphisms on paroxetine treatment (Gex-Fabry et al. 2008). Several studies of the association of ABCB1 polymorphisms and the response to citalopram, duloxetine or escitalopram treatment showed controversial results (Lin et al. 2011; Menu et al. 2010; Nikisch et al. 2008; Perlis et al. 2010). Studies concerning the effect of the aforementioned 5-HTTLPR on antidepressant treatment response also revealed contradictory results (Keers et al. 2011; Lewis et al. 2011; Strohmaier et al. 2011; Taylor et al. 2010). However, a recent simulation trial found an increased antidepressant response and tolerability of drug treatment, when the drug choice was based on 5-HTTLPR genetic testing compared to clinician's decision (Serretti et al. 2011).

Two GWAS including 339 patients of the MARS sample and 361 patients of an independent replication sample, and the genotyping of a set of 328 SNPs in 832 patients of the STAR*D sample found no significant associations with single genes, but the high or low occurrence of "response-alleles" was able to predict the response to antidepressant treatment (Ising et al. 2009). Seminal results from Dex/CRH and other HPA axis studies have increased our understanding of the neurobiological mechanisms of antidepressant response. Compared to these data, the findings from genetic studies including GWAS, are disappointing to date. Ongoing and future studies with larger sample sizes are designed to detect more specific genetic determinants of response to antidepressant treatment (Williams et al. 2011).

Pharmacotherapy of altered stress axis activity

The quest for drugs that specifically target stress axis activity and thereby exert an antidepressant effect seems to be a promising approach. Recently, it has been reported that sertraline increases human hippocampal neurogenesis via a GR-dependent mechanism (Anacker et al. 2011). Most antidepressants have a pronounced but non-specific normalizing effect on HPA activity and stress hormone release (Mason and Pariante 2006; Schüle 2007). In addition, different classes of psychopharmacological drugs interfere with HPA regulation (Table 1).

- Table 1 about here -

The anxiolytic effect of benzodiazepines is associated with a downregulation of the CRH system (Skelton et al. 2000). Oxytocin (OXT) is a peptide hormone that is synthesized in the same hypothalamic nuclei and follows similar neural and extracellular distribution as AVP. Both hormones are seen as functional antagonists concerning the regulation of the stress response. In contrast to AVP, OXT inhibits the HPA axis under stress conditions, reduces amygdala hyperactivity and anxiety and enhances social behavior (Heinrichs et al. 2003; Meyer-Lindenberg 2008; Meyer-Lindenberg et al. 2011; Zak et al. 2007). Although alterations in levels of plasma OXT correlate with anxiety and affective symptoms in depression (Cyranowski et al. 2008; Scantamburlo et al. 2007), an antidepressant effect of OXT is not known (Stein 2009) . Interestingly, previous studies in hyper-anxious rats have shown that the CRHR1 antagonist R121919 attenuates the stress-induced release of oxytocin indicating that the CRHR1 plays a critical role in medating the stress-induced alterations in plasma oxytocin (Keck et al., 2003a).

Neurosteroids have neurochemical and behavioral properties comparable to benzodiazepines. Anxiolysis and stress reduction may be induced via an agonist action on gamma-aminobutyric acid $(GABA)_A$ receptors (Rupprecht and Holsboer 1999). Interestingly, different drugs such as clozapine, gamma-hydroxybutyrate (GHB) (Barbaccia 2004; Bosch et al. 2011) and the

anxiolytic ligand of the translocator protein XBD173 (Rupprecht et al. 2009) induce neurosteroid synthesis and secretion. Whether a direct or indirect increase of the biological activity of neurosteroids may relieve symptoms of depression is unclear.

In the past years, several strategies have been tested to directly reduce HPA activity in patients with depression. GR-antagonists were applied with the aim to normalize possible MR/GR imbalances in stress-related depression. In vitro and animal studies indicate that several specific GR antagonists and a highly selective AVP (V1B) receptor antagonist could have stress protective and antidepressant effects (Bachmann et al. 2003; Griebel et al. 2002; Serradeil-Le Gal et al. 2002). The broad evidence for an association of a central CRH/CRHR1 hyperactivity and symptoms of anxiety and depression led to the hypothesis of the potential efficacy of specific CRHR1 antagonists in these and other stress-related disorders (Grigoriadis 2005). Antalarmin, the first available CRHR1 antagonist, was effective in attenuating the response to stress in monkeys (Habib et al. 2000). Moreover, the selective CRHR1 antagonist NBI-30775/R121919 reduced anxiety-like behavior in rats (Heinrichs et al. 2002; Lancel et al. 2002), while the selective CRHR1 antagonist CP-154,526 exerted this effect in mice (Griebel et al. 1998).

In a first clinical trial over a period of 30 days, NBI-30775/R121919 exerted dose-dependent antidepressant and anxiolytic effects which were comparable to paroxetine (Holsboer and Ising 2008; Künzel et al. 2003; Zobel et al. 2000). In healthy subjects the selective CRHR1 antagonist NBI-34041 leads to an inhibition of the HPA axis during the Trier Social Stress Test (Zimmermann et al. 2004). However, with regard of the potential antidepressant effects of CRHR1 antagonists, the results remain largely negative: a study with the selective CRHR1 antagonist CP 316.311 failed to show beneficial effects compared to sertraline and placebo (Binneman et al. 2008) and three trials with the progesterone receptor/GR antagonist mifepristone did not show antidepressant effects compared to placebo (Schüle et al. 2009).

Possible reasons for the failure of these drugs in antidepressant trials may result from the complexity of the pathophysiology of the HPA axis and the limited diagnostic tools. There is no existing biomarker that is able to detect an increased central CRH/CRHR1 signaling (the Dex/CRH-test reveals dysbalances of the gross HPA activity), and thus to identify patients that would possibly benefit from such treatment. Moreover, the stress response is a highly adaptive system that might largely compensate pharmacological interventions. Given, that genetic, epigenetic, neuroendocrine and other factors such as immunologic influences including their complex interactions play a role in the pathophysiology of stress-related depression, the probability of remission due to a single receptor antagonist treatment seems low. However, the blockade of central CRHR1 can be regarded as a first step towards a personalized psychiatric therapy, as this treatment targets specific pathophysiological alterations underlying depressive symptoms (Holsboer 2008; Holsboer and Ising 2010).

Conclusions

During the past decades, a broad spectrum of pharmacological treatments for depressive disorders has become available. However, the overall efficacy of these treatments remains unsatisfactory. Thus, a focus of research is not only to improve treatment options, but also to identify the factors that determine antidepressant treatment response with a special emphasis on neuroendocrine and genetic factors. Genetic research – apart from few recent G x E and epigenetic studies – has produced unsatisfactory results to date, demonstrating the high complexity of genotype-phenotype interactions in affective disorders. In this regard, the HPA system may serve as a useful marker, even with predictive potential for remission and risk of subsequent relapse. However, the current knowledge is still limited and direct translation from genotype to therapy may not be expected in the near future. Further basic and clinical research is needed to establish and validate biomarkers for the identification of biologically

characterized specific subgroups of patients in specific disease phases to keep the promise of personalized treatment in psychiatry.

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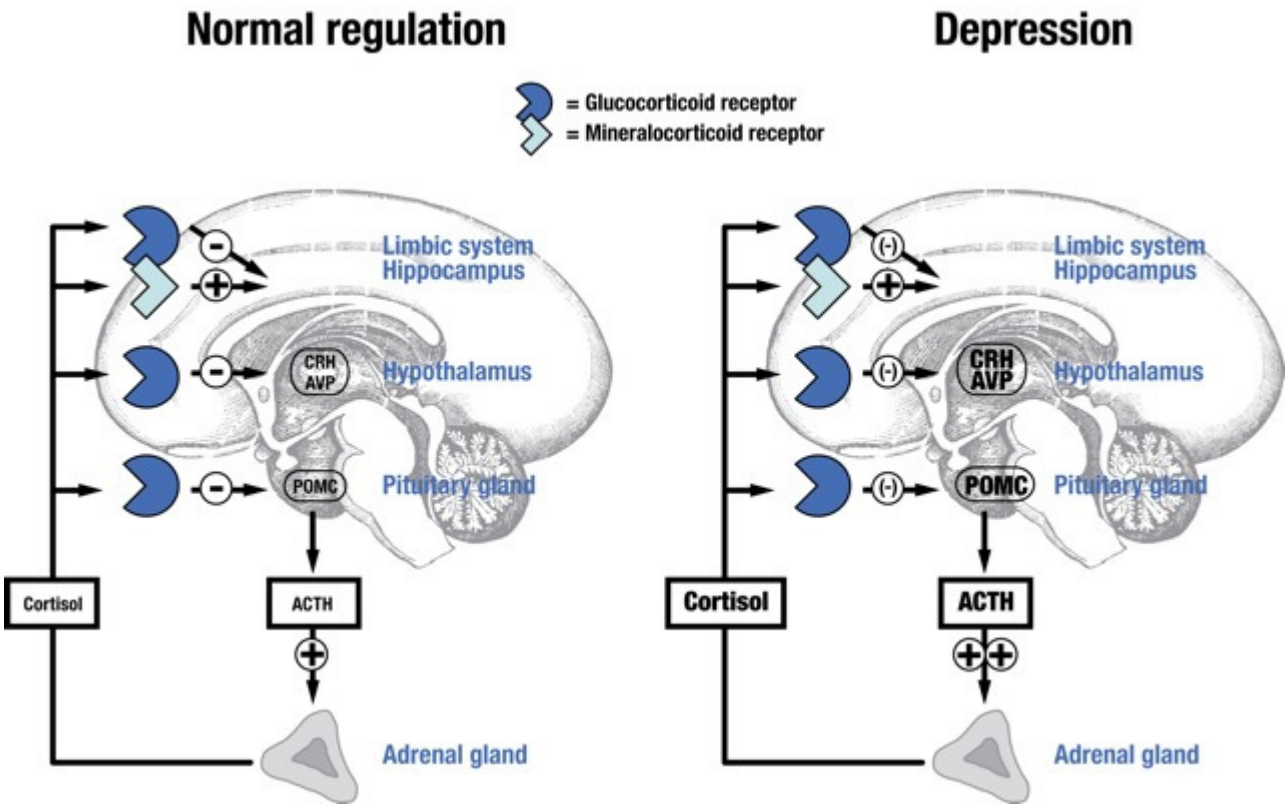
Table 1 Effects of selected psychopharmacological drugs on HPA activity.

Drugs	**Effect**
Citalopram (SSRI)	Normalization of HPA activity partly correlates with antidepressant effect (humans)
Venlafaxine (SNRI)	
Mirtazapine (α2 receptor antagonist)	
Moclobemide (MAO-I)	
Alprazolam (GABA-A agonist)	Anxiolytic (animal/human), CRH system ↓
Oxytocin (neuropeptide)	Prosocial (animal/human), HPA activity under stress ↓
3,5-THP (neurosteroide, $GABA_A$ agonist)	Anxiolytic (animal/human), CRH system ↓, neurosteroidogenesis induced by clozapine and gammahydroxybutyrate (GHB)
Mifepristone (progesterone receptor - and GR antagonist)	Antipsychotic in patients with Cushing syndrome and depression with psychotic symptoms (human)
Org 34850 (specific GR antagonist as augmentation to SSRI)	Desensitization of serotonin 1A ($5\text{-}HT_{1A}$) receptors, downregulation of presynaptic serotonin transporters (animal)
Antalarmin (selective CRHR1 antagonist)	Anxiolytic (mice), proexplorative und prosexual (monkeys)
NBI-30775/R121919 (selective CRHR1 antagonist)	Anxiolytic (diverse species/human), sleep enhancing (rat/human), antidepressive (human)
NBI-34041 (selective CRHR1 antagonist)	HPA activity under stress ↓
CP 316.311 (selective CRHR1 antagonist)	No antidepressive effect (human)
SSR149415 (selective AVP V1B receptor antagonist)	Anxiolytic (diverse species), antidepressant-like (diverse species)

For abbrevations see pages 2-3.

Figure 1 Concept of normal HPA axis regulation (left side) and dysregulation in depression (right side).

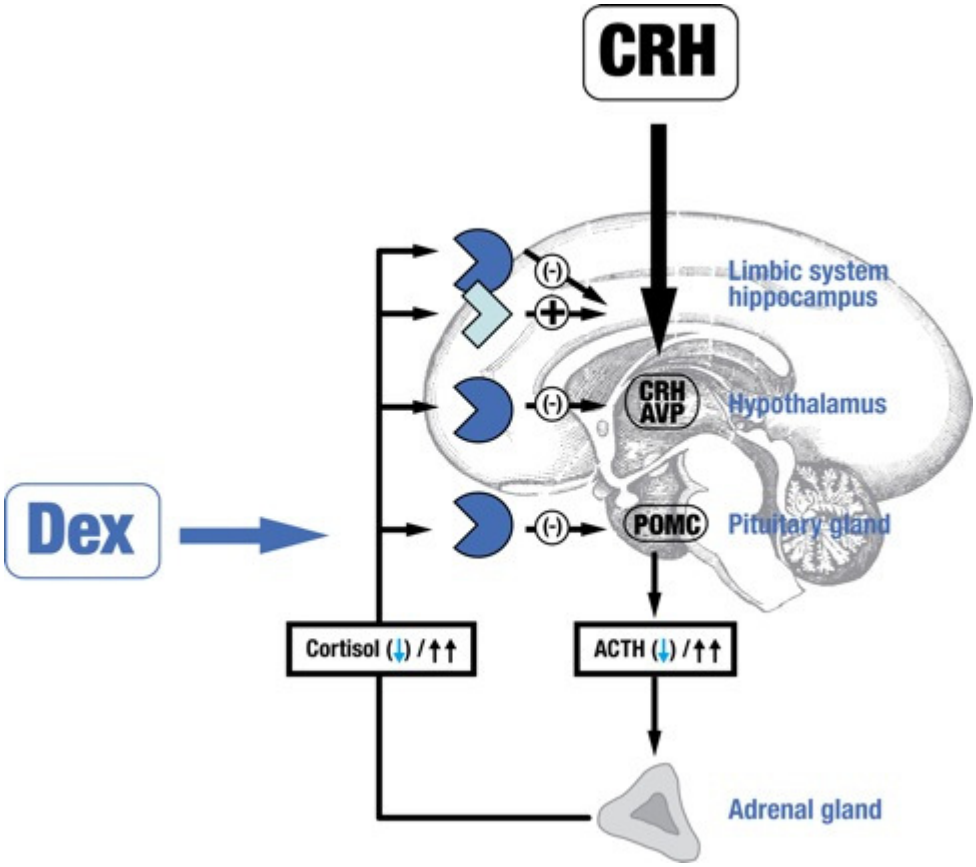


Legend to Figure 1

Under physiological conditions, cortisol stimulates central glucocorticoid receptors leading to an inhibition of CRH and AVP release. In depression, impaired corticosteroid signaling results in an attenuation of the negative feedback inhibition, which may result in CRH and AVP overactivity (hypothalamus) and increased ACTH release from the anterior pituitary leading to chronically elevated cortisol levels.

HPA: hypothalamic-pituitary-adrenal; CRH: corticotropin-releasing hormone; AVP: arginine vasopressin; POMC: proopiomelanocortin; ACTH: adrenocorticotrope hormone. Modified after Ising and Holsboer 2006.

Figure 2 Dexamethasone/CRH-test.



Legend to Figure 2

Procedure of the Dex/CRH-test: 1. oral application of 1.5 mg dexamethasone at 11:00 p.m. (maximal inhibition of ACTH/cortisol release); 2. Assessment of morning basal cortisol on the following day; 3. I.v. application of 100 µg human CRH at 3:02 p.m. (maximal stimulation of ACTH/cortisol release); 4. Six blood samples in intervals of 15 minutes are taken until 4:30 p.m. for the assessment of ACTH and cortisol plasma levels.

Dex: Dexamethason; HPA: hypothalamic-pituitary-adrenal; CRH: corticotropin-releasing hormone; AVP: arginine vasopressin; POMC: proopiomelanocortin; ACTH: adrenocorticotrope hormone.