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Stress, hypercortisolism and corticosteroid receptors in depression: implicatons for therapy☆

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Abstract

Clinical and preclinical studies have gathered substantial evidence that alterations of the stress hormone system play a major, causal role in the development of depression. In this review article, a summary of studies sustaining that view is given and data are presented which demonstrate that depression is associated with an impairment of corticosteroid receptor function that gives rise to an excessive release of neurohormones to which a number of signs and symptoms characteristic of depression can be attributed. The studies referred to in the following unanimously support the concept of an antidepressant mechanism of action that exerts its effects beyond the cell membrane receptors of biogenic amines and particularly includes the improvement of corticosteroid receptor function. When activated by ligands, corticosteroid receptors act as transcription factors in correspondence with numerous other transcription factors already known to be activated by antidepressants. Furthermore, the potential of drugs that interfere more directly with stress hormone regulation, such as corticosteroid receptor antagonists and corticotropin-releasing hormone receptor antagonists, is discussed.

Keywords: Stress; Depression; HPA system; Corticotropin-releasing hormone; Antidepressants

1. Introduction

The concept of ‘stress’ generally refers to physical or psychological events capable of disrupting homeostasis. The response to stress involves a number of processes comprising what was termed by Hans Selye the ‘general adaptation syndrome’. The key neuroendocrine component of this response to stress is the hypothalamic–pituitary–adrenocortical (HPA) system, which acts as an interface between cognitive and non-cognitive (e.g. inflammatory) stressors processed in the CNS and the peripheral endocrine response system, the latter being dominated by the pituitary–corticotrophic–adrenocortical axis. Various stress-related inputs converge in nuclei of the hypothalamus. In the paraventricular nucleus (PVN) of the hypothalamus neurons are located that synthesize

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corticotropin-releasing hormone (CRH), vasopressin and other neuropeptides, which have the potential of exerting diverse humoral, autonomic and behavioral effects. Some of these neuropeptide-containing neurons project to the external layer of the median eminence, where they release CRH or vasopressin into the portal circulation, which bind to anterior pituitary corticotrophs and induce the synthesis and release of corticotropin (ACTH). ACTH, in turn, activates the biosynthesis and release of corticosteroids, especially cortisol, the major glucocorticoid hormone in humans, from the adrenal cortex. These hormones have numerous diverse actions which are necessary for adaptation to an acute challenge. Cortisol, for example, enhances the availability of glucose, the major nutrient of the brain. A fine-tuned homeostasis of the HPA system is important because no other molecule in the organism is secreted at a comparably wide concentration range into the circulation than cortisol. Transducing these wide concentration ranges, which also allow circadian rhythms, into coordinated actions at various targets, of which the brain is the largest, requires many checks and balances to prevent the deleterious effects of inappropriate corticosteroid secretory activity both at resting condition or following stress exposure. Hypercortisolism has already been observed in patients with depression for a long time. However, this neuroendocrine alteration was initially interpreted as reflecting the hormonal stress response that was only secondary to the suffering of patients who experience a depressive episode. Later on, it was realized that acute life events, such as the loss of a partner or a close person or severe professional difficulties may induce depression in individuals susceptible to become affected. In this context, the hyperdrive of the HPA system was either perceived as a trigger of a depressive episode or as a neuroendocrine response to it.

More recently, the scene has changed and evidence has accumulated which supports the notion that the mechanism driving the HPA system is causally related to the mechanism underlying depression, and, moreover, that the fine-tuned regulatory system of this neuroendocrine system provides targets for pharmacotherapeutic and even psychotherapeutic interventions (Holsboer and Barden, 1996).

2. Clinical studies

The first studies suggesting a causal relationship between disturbances of HPA regulation and psychopathology were performed at the Department of Psychiatry of the Ludwig-Maximilians-Universität in Munich. They included the repeated performance of the dexamethasone-suppression test (DST) in patients suffering from a depressive episode (Holsboer et al., 1982). This simple neuroendocrine tool consists in the administration of a low dose (1–2 mg) of dexamethasone at 23:00 h and the measurement of cortisol levels at one or more time points on the following day. Dexamethasone acts at corticotrophic cells by binding to glucocorticoid receptors which, through negative response elements in the promoter region of the proopiomelanocortin (POMC) gene, inhibit the expression of this gene and, subsequently, the synthesis and secretion of ACTH. In turn, the suppression of ACTH through dexamethasone prompts a decrease of corticosteroid secretion (cortisol in humans and corticosterone in rats and mice). In healthy controls, the appropriate response that follows is a suppression of ACTH and cortisol. The parameter that is measured by this test is the capacity of the glucocorticoid receptors of pituitary corticotrophs to exert a negative regulatory effect on the release of ACTH and, consequently, cortisol. Thus, patients who have inappropriately suppressed plasma cortisol levels, i.e. who escape from the suppressive effect of dexamethasone, have an incapacitated glucocorticoid receptor function. This impairment can be primary, i.e. genetically derived, or secondary, i.e. caused by an enhanced ACTH and cortisol secretion, which leads to glucocorticoid receptor desensitization. First longitudinal studies in patients treated with a variety of different antidepressants showed that in all those cases in which the suppressive action of dexamethasone was demonstrated to be reduced, i.e. where plasma cortisol levels were increased despite dexamethasone administration, the resolution of depressive psychopathology was preceded by the return to an appropriate suppression. In turn, those patients who seemed to be remitted according to psychopathology assessments, but who had repeatedly abnormal dexamethasone test results, proved to be at high risk for relapse (Fig. 1).

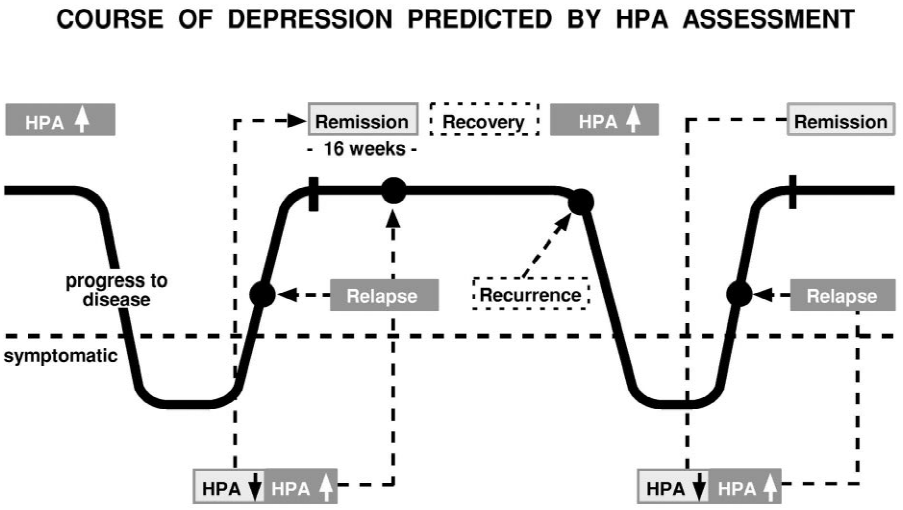

Fig. 1. Postulated relationship between the course of depression and HPA system regulation.

These early observations suggested that development of HPA dysregulation precedes depressive symptomatology rather than being a consequence of it. However, repeated DST performances were of only limited use for routine clinical monitoring because of the low sensitivity of the test (i.e. abnormal test results although the criteria for major depression were fulfilled), which is in the range of about 20–30%. After corticotropin-releasing hormone (CRH) became available for clinical studies, the DST was combined with CRH administration, and the resulting dexamethasone–CRH test proved to be much more sensitive (above 80%) in detecting HPA system alterations (Heuser et al., 1994) than the DST. Several studies show that patients pretreated with dexamethasone react by an exaggerated ACTH and cortisol response when a fixed dose of 100 μg human CRH is injected (Fig. 2).

Modell et al. (1997) administered three different dosages of dexamethasone prior to CRH infusions in patients with depression and controls and showed that the dose–response curve was shifted into a direction that is best explained by a decreased corticosteroid receptor sensitivity (Fig. 3).

The clinical implications for a continued glucocorticoid receptor deficit in depression were also demonstrated by studies showing that there is a direct relation between a patient's response to therapy and the individual test outcomes, which reveal a gradual normalization of the response of the HPA system to the dexamethasone–CRH test during the clinical course towards remission (Holsboer-Trachsler et al., 1994; Heuser et al., 1996). In contrast, in those patients who did not respond to therapy or who responded but had a relapse into depression within an observation period of about 6 months, a persistent abnormal HPA system response to the combined dexamethasone–CRH test was found (Zobel et al., 1999, 2000) (Fig. 4).

Numerous studies in humans and rats have helped to clarify the mechanism involved in the paradoxical surge of ACTH and cortisol secretion that is observed in depressive patients subjected to the combined dexamethasone–CRH-test. When dexamethasone is administered at pituitary corticotrophs at the low dosages used in this test, it has only limited access to the brain, because it is a substrate for a multidrug resistance gene (mdr) product, a P-glycoprotein, which prevents the blood–brain barrier passage of dexamethasone. As a result peripheral cortisol levels are decreased by the ACTH-suppressing action of dexamethasone at the pituitary corticotrophs, and corticosteroid receptors in the brain are thus deprived from their natural ligands. As dexamethasone induces but does not compensate for this loss, the brain is led to interpret this situation as an adrenalectomy-like condition and therefore responds with an excessive release of ACTH sec-

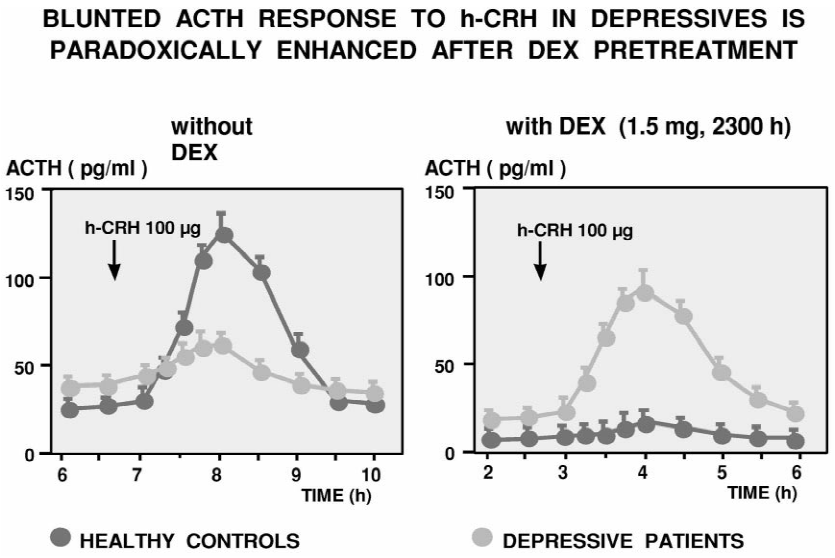

Fig. 2. Patients with depression usually show a blunted ACTH response to CRH, which is believed to be secondary to desensitized CRH_1 receptors (left). After pretreatment with a low dose of dexamethasone, healthy controls do not show a substantial ACTH release, whereas the ACTH response of patients with depression is comparable to the response of healthy controls not pretreated with dexamethasone (right).

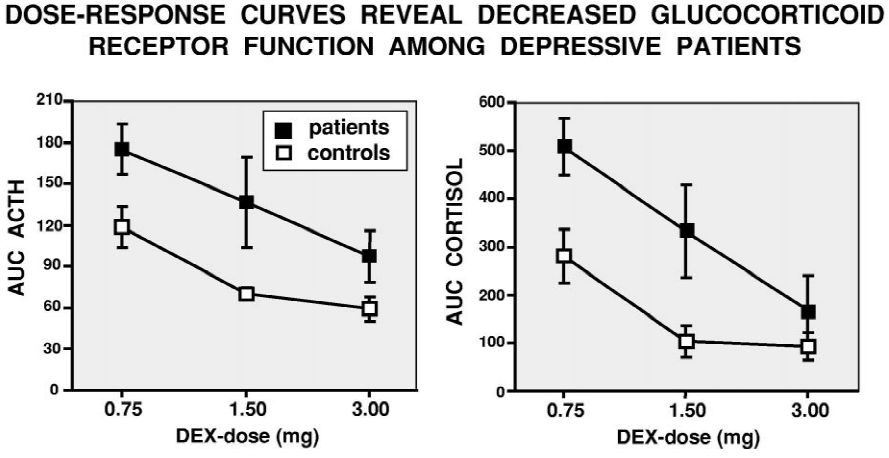

Fig. 3. In 30 patients with major depression three different dosages of dexamethasone (DEX) (given orally at 23:00) had a less suppressive effect on ACTH and cortisol release (both expressed as area under the time course curve, AUC) than in the group of matched controls, which indicates an impaired corticosteroid receptor function in depressed patients (from Modell et al., 1997).

retagogues, including vasopressin (AVP). If CRH is administered under the dexamethasone pretreatment condition, CRH and AVP are capable of synergizing their effects to override the suppressive effect of dexamethasone (von Bardeleben et al., 1985). In patients with depression, corticosteroid receptor function is either genetically altered, as the Munich Vulnerability Study (Holsboer et al., 1995; Modell et al., 1997, 1998) suggests, or acquired as a result of impaired coping with stress, and this is why these patients show a much less restrained release of central ACTH stimulants than healthy controls or depressive patients in remission.

Since CRH neurons project from the hypothalamic

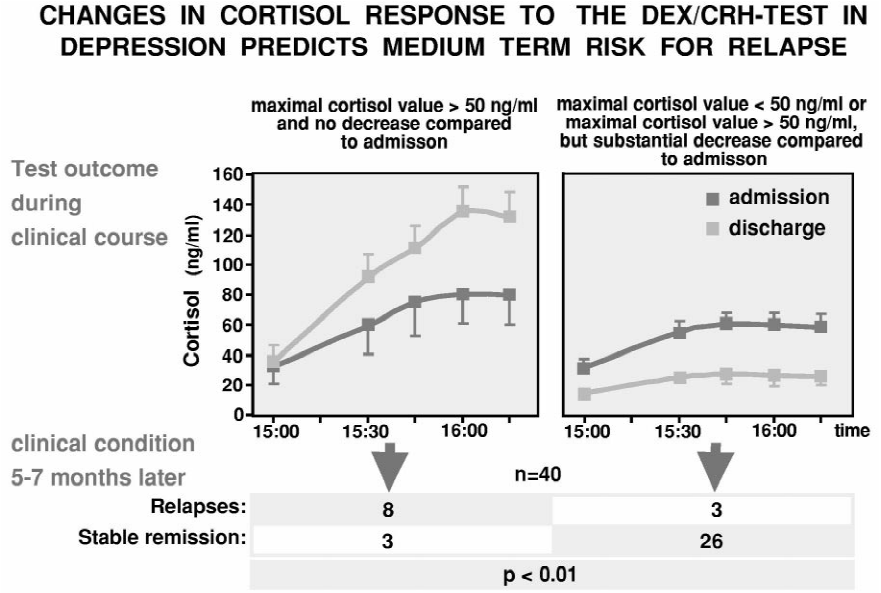

Fig. 4. Patients who have normal or substantially decreased cortisol levels after Dex–CRH testing have a better short-term prognosis for about 6 months than patients with a constantly increased HPA system regulation (from Zobel et al., 1999).

PVN to many brain areas, including the median eminence, where CRH is released into the portal circulation and carried to the CRH receptors of the pituitary corticotrophs, it was important to demonstrate that CRH gene expression and secretion is negatively controlled by ligand-activated glucocorticoid receptors which, if defunct, are unable to suppress CRH release, so that a CRH hypersecretion may be expected to emerge. First indirect evidence for such a possibility came from studies in which human CRH was intravenously injected and the ACTH response measured. The first studies in which a CRH test was applied agreed that the ACTH response to CRH is blunted in depression, provided CRH is injected in the afternoon when the endogenous HPA activity is low (Holsboer et al., 1986). This finding was in accordance with a CRH-receptor desensitization secondary to continuously increased hypothalamic CRH secretion. The interpretation of blunted ACTH response as reflecting increased CRH release was strengthened by data of Nemeroff et al. (1984), showing that CRH is elevated in the cerebrospinal fluid of patients with depression. Whereas it is not entirely clear whether CRH measured in the CSF is reflecting hyperactivity of CRH neurons in those brain areas which are likely to be involved in the pathogenesis of depression, these data are consistent with the view of a disturbed regulation of CRH release. They are also strengthened by another finding made by the group of Charles Nemeroff, who discovered that CRH binding in the prefrontal cortex is diminished in suicide victims who had suffered from depression (Nemeroff et al., 1988). This decrease in receptor binding was interpreted as evidence for a homologous desensitization of CRH receptors secondary to increased secretion of CRH into these brain areas. More recently, the notion of a hyperactive neuronal activity was supported by findings of the group led by Dick Swaab in Amsterdam, who showed that the number of CRH secreting neurons was strongly increased in patients with depression who had committed suicide (Raadsheer et al., 1994) (Fig. 5).

Taken together, these clinical studies have provided compelling evidence that corticosteroid receptor function, thought to be the key element of a balanced HPA-system regulation, is impaired and, as a consequence, secretion of CRH and other ACTH-eliciting secretagogues elevated. Moreover, this disturbance seems to be responsive to therapeutic

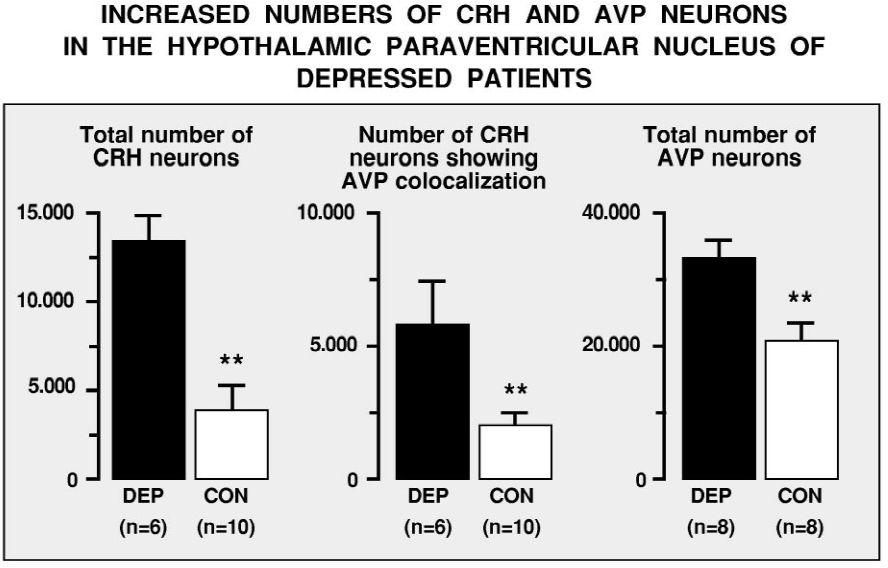

Fig. 5. Patients with major depression have an increased number of CRH and arginine vasopressin (AVP) neurons and also increased copackaging of CRH and AVP in PVN neurons, which explains the excessive HPA activity in these patients as both neuropeptides synergize their actions at pituitary CRH_1 receptors. DEP, depressed patients; CON, controls (adapted from Raadsheer et al. (1994) and Purba et al. (1996).

interventions, and the questions that have been transferred from clinical research into preclinical laboratories were the following: (1) does the HPA hyperdrive account for depressive symptomatology, and, if so, which neurohormones are responsible? (2) At which sites of the complex regulatory systems do antidepressants interfere? (3) How can drug targets be identified that allow a more direct intervention?

3. Preclinical studies

Only a few neuropeptides have been studied more extensively than CRH with regard to their behavioral effects and their possible implications for psychopathology. Soon after CRH became available for experimental studies, studies in rats and monkeys supported the view that CRH is a major coordinator of the response to stress and that the behavioral changes induced by CRH are independent of its actions on the HPA system. CRH, when given to rats intracerebroventricularly (i.c.v.), induces a number of anxiety-related modes of behavior. These include the CRH-induced potentiation of acoustic startle, suppression of social interaction and an increase in stress-induced freezing behavior. Symptoms of behavioral despair were also observed in adult rhesus monkeys. As shown in Fig. 6, most of the signs and symptoms induced by CRH administration correspond to symptoms of today's diagnostic algorithms.

All of the experiments in which CRH has either been administered i.c.v. at high dosages or to specific brain areas produced increased anxiety-related behavior in normal rats. More recently, the possibility of studying the effects of decreased CRH neurotransmission by administering antisense oligodeoxynucleotides (ODN) corresponding to the start-coding region of the CRH mRNA was created (Fig. 7).

The application of this kind of gene therapy to stressed rats produced a decrease in CRH biosynthesis and led to a reduction of the whole spectrum of anxiety-related patterns of behavior. Another molecular approach was used by Stenzel-Poore et al. (1994), who generated transgenic mice overexpressing CRH. These mice have deficits in emotionality and were used as genetic models of anxiogenic behavior. It was possible to inhibit most of the CRH-elicited anxiety-related modes of behavior by

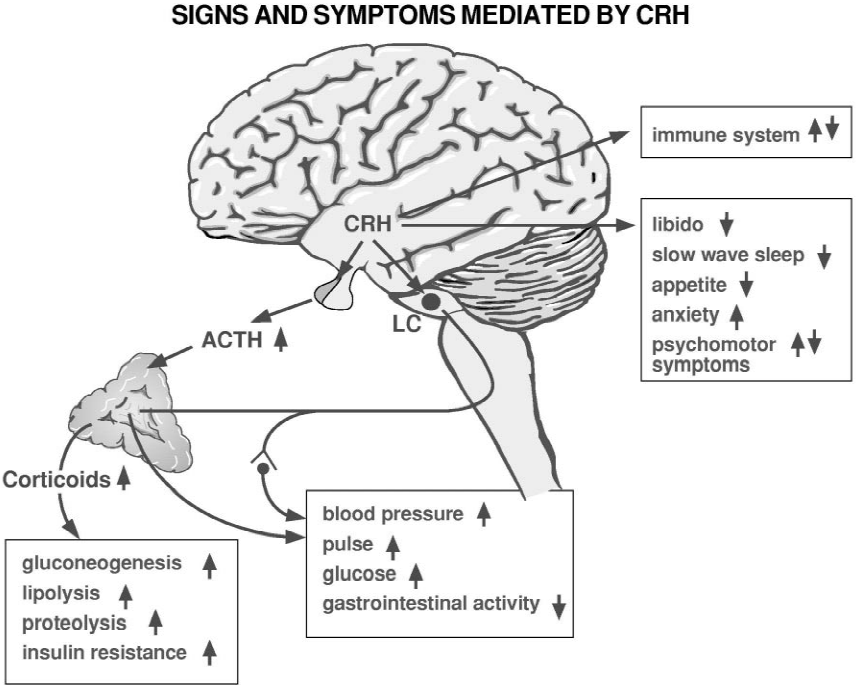

Fig. 6. Animal studies in which CRH was injected intracerebroventricularly or in which CRH synthesis was disrupted (knockout mice or antisense oligodeoxynucleotide treatment of rats) or CRH receptor function manipulated through antagonists, gene therapy or gene targeting are in accord with indirect clinical evidence that many signs and symptoms present in depression can be attributed to enhanced secretory activity of central CRH.

administration of α-helical CRH_{9-41}, a peptidergic CRH-receptor antagonist with unspecific properties regarding the different CRH receptor subtypes and burdened with its own intrinsic effects. Therefore, the group of Rainer Landgraf in Munich used the antisense technique to identify the particular receptor subtype most likely to present a target for compensating the pathogenetic effects of the postulated CRH hyperdrive (Liebsch et al., 1999). Comparison of the behavioral effects of antisense probes that were either directed against CRH_1- or against CRH_2-receptor mRNA suggested that CRH_1 receptors are more likely to convey anxiety and, possibly, depression-related signalling. The CRH_1-receptor knockdown through antisense probes clearly supported the notion that CRH_1-receptors are a much more likely target for drug intervention than CRH_2-receptors, and complementary evidence was provided by the generation of a CRH_1-receptor-deficient mouse mutant by the group of Wolfgang Wurst in Munich (Timpl et al., 1998). According to the localization of CRH in the brain and the finding that CRH-induced anxiety-related behavior can be decreased by CRH_1 antisense treatment, CRH_1 receptor-deficient mice should prove to be less anxious than normal mice. It turned out, indeed, that mutant animals with a CRH_1-receptor deletion, when they were given the choice between entering a dark or a brightly lit compartment of a test box, spent more time in the brightly lit compartment than the control mice (Fig. 8).

Bright light presents a hostile condition for nocturnal animals, such as mice, and as Timpl et al. (1998) showed, CRH_1 receptor-deficient mice are less anxious, and there is no other system, for example the highly homologous CRH_2 receptor, that could compensate the lacking CRH_1 receptor function as an important behavioral component of the stress response. These findings were supported by a study of Smith et al. (1998), who showed similar effects in a similar CRH_1 receptor-knockout mouse model. Based upon these findings, it seemed reasonable for

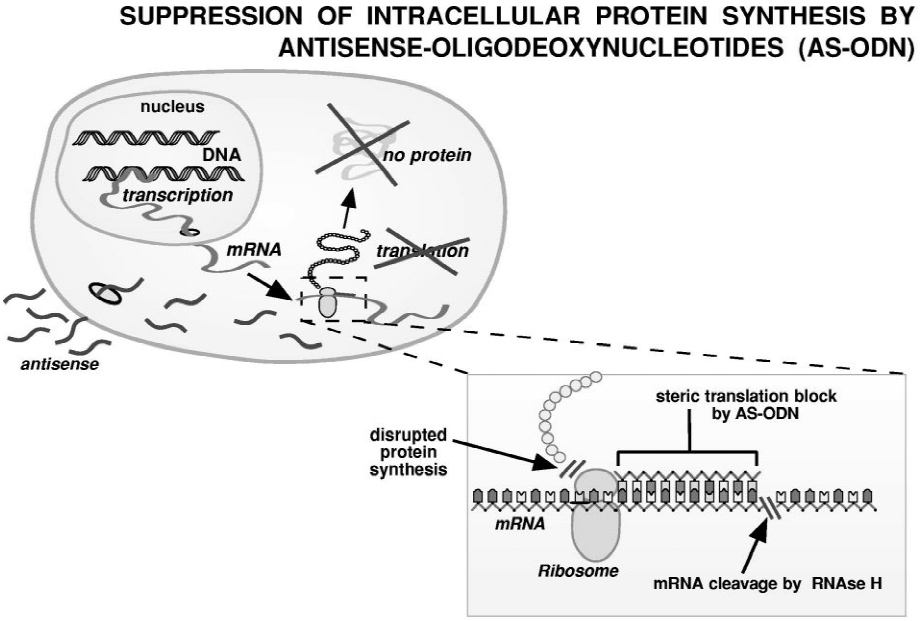

Fig. 7. If antisense oligodeoxynucleotides are administered, mRNA cannot be translated into protein because of a steric translation block which results in mRNA degradation.

pharmaceutical companies to develop a lead compound which partially antagonizes the CRH_1 receptor in order to suppress the deleterious behavioral sequelae of an unrestrained overactivity of CRH neurons. Such a compound needs to exert its effects via oral administration, i.e. it must not be degraded by peripheral metabolism and it must pass the blood–brain barrier. Compounds containing the pyrrolopyrimidine moiety in their molecular structure were found to fulfil the desired requirements (Fig. 9).

4. Antidepressant action

In order to judge whether blocking of CRH_1 receptors may indeed constitute a novel antidepressant mode of action, it is helpful to briefly reevaluate the pharmacology of established antidepressant drugs. The spectrum of mechanisms through which antidepressant compounds may exert their effects is wide, and potential candidate mechanisms, including actions beyond cell membrane receptors, are being elucidated at a fast rate. The mechanisms of action of antidepressants almost always include interactions with presynaptic uptake transporters of biogenic amines, such as the selective serotonin-reuptake inhibitors (e.g. fluoxetine, citalopram, paroxetine), the noradrenaline-reuptake inhibitors (e.g. desmethylimipramine, reboxetine), compounds that have a variety of diverse actions (amitriptyline, venlaflaxine, mirtazapine) or monoamine oxidase inhibitors (e.g. tranylcypromin, moclobemide). While some progress has been made by developing drugs with a more specific action and less side effects, a major breakthrough has still to be achieved with regard to efficacy and the protracted time until the onset of clinical action. What is puzzling is that the drugs on the market, despite their vast variety of pharmacological effects, have a rather uniform clinical profile with a drug response of 70–80% and a time-to-onset span that ranges between 2 and 6 weeks. These figures can be confirmed even if drugs are compared that have opposite effects on the serotonin-uptake transporters as, for example, tianeptine, which enhances serotonin reuptake, and paroxetine, which inhibits reuptake (Nickel et al., unpublished). In the light of the current status of antidepressant drug

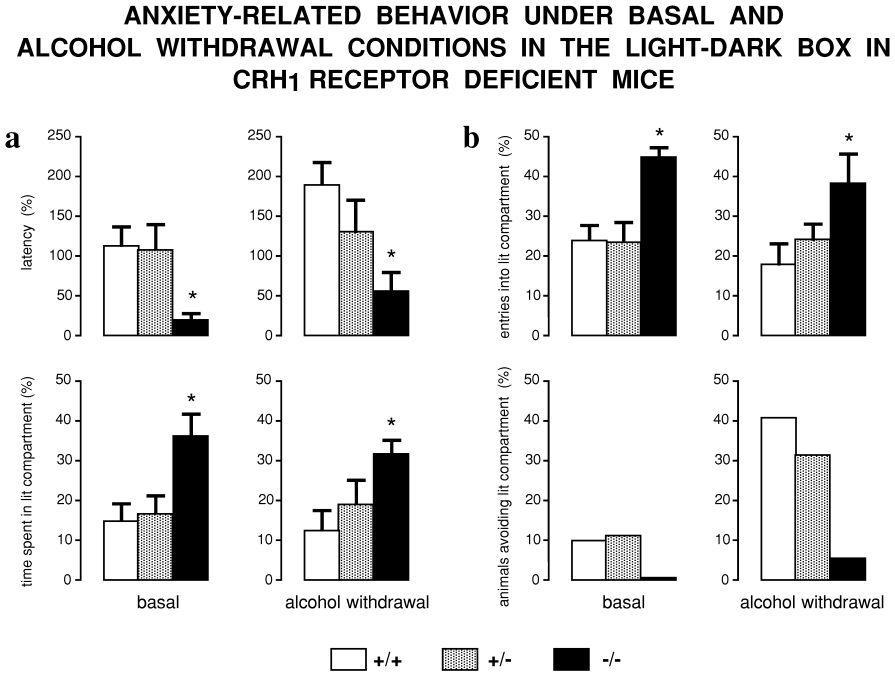

Fig. 8. Time (latency) that elapsed until the lit compartment was entered is decreased and the time spent in the lit compartment is increased in CRH_1 receptor-deficient mutants (a). After all mice had been subjected to a forced alcohol-drinking procedure and subsequent withdrawal from alcohol, the anxiety-related behavior (latency and time spent in lit compartment) reflected a gene/dosage effect with the intensity of anxiety increasing with increasing CRH_1 receptor levels (wild-type > heterozygous > homozygous). Similar effects were observed when anxiety-related behavior was assessed by scoring the entries into the lit compartment (b, upper panel) or by counting those animals that avoided the lit compartment (b, lower panel) (adapted from Timpl et al., 1998).

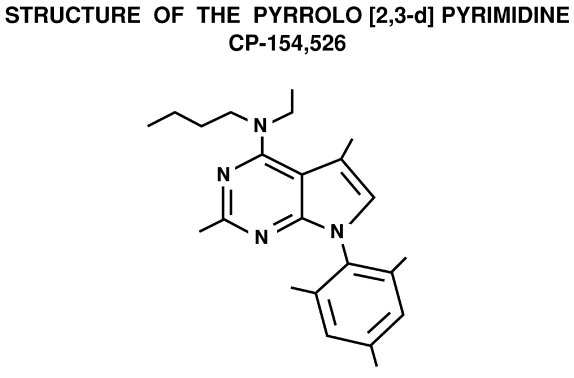

Fig. 9. High speed screening of compound libraries with a radioligand binding assay led to the discovery of a low affinity lead compound, which, after several chemical modifications, resulted in the discovery of CP-154,526 (butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3*d*]pyrimidine-4-yl]ethylamine), which binds with high affinity to cerebral cortical ($K_i = 5{,}7$ nM) and pituitary ($K_i = 1.4$ nM) membranes of rats (from Schulz et al., 1996).

development it seems fair to say that the relevant mechanisms induced by these drugs are more downstream, i.e. they exert effects on the intracellular signalling cascade and adaptive processes related to changes in profiles of expression of a variety of genes (Fig. 10).

In the context of the stress system as a potential target for drug intervention, it is important to note that the CRH promoter region, where transactivation of CRH gene expression or its repression are coordinated, contains a sequence to which phosphorylated cyclic AMP response element-binding protein (CREB) binds (Spengler et al., 1992). This protein is constitutively present in cells and only assumes its function via phosphorylation by protein-kinase A. This enzyme transfers a phosphate moiety to the protein, which subsequently binds to a cyclic AMP response element (CRE) and afterwards transactivates genes that carry a CRE sequence in their promoter region. When an antidepressant is given

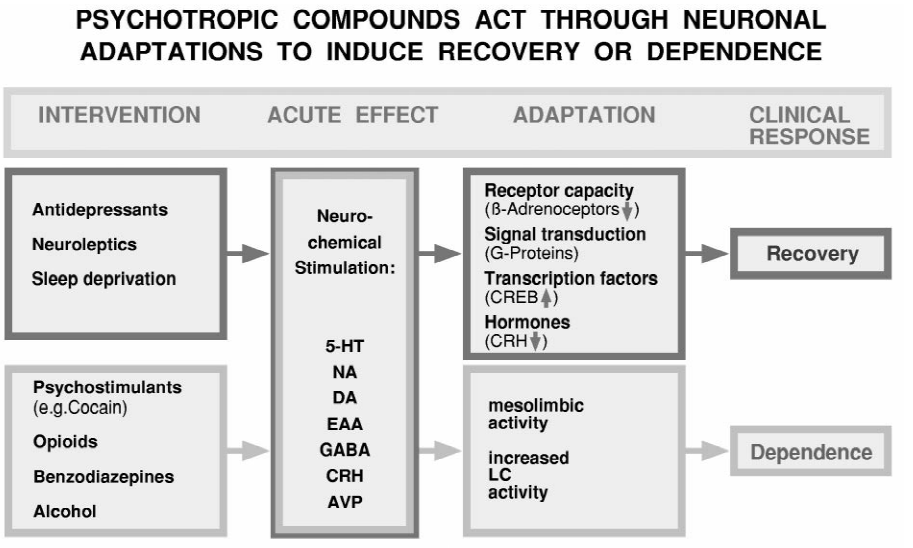

Fig. 10.

that, for example, blocks the presynaptic norepinephrine-uptake transporter, the norepinephrine bioavailability at postsynaptic adrenoceptors is increased. This prompts an initially increased activation of cyclic AMP and protein-kinase A activity with a number of changes in gene expression, including those of CRE-regulated genes. However, after long-term exposure to elevated norepinephrine, adrenoceptors become desensitized, and this is followed by a decrease in the intracellular cyclic AMP pool, a decrease in protein-kinase A activation, and finally a decrease in the activation of those genes that are positively regulated through CREs. Since the promoter region of the CRH gene contains such a CRE, it seems plausible to assume that long-term antidepressant treatment through desensitization of cell membrane-bound β-adrenoceptors lowers the degree to which CREB is phosphorylated and that CRH expression is consequently decreased (Fig. 11).

This effect, of course, is not a straightforward one and includes a number of checks and balances whose exact nature has not yet been elucidated. What has been found in patients remitted from depression, however, is a decrease of their HPA hyperactivity and a decrease in the concentration of CRH in the CSF, both of which are numerously replicated findings that are consistent with the concept of a mechanism that decreases CRH gene expression (Owens and Nemeroff, 1992). The exact molecular mechanism by which CRH_1 receptors are modulated by antidepressants is still being investigated, with the particular difficulty of these studies lying in the complex nature of the respective CRH_1-receptor gene promoter.

Other powerful regulators of gene expression are corticosteroid receptors, namely the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which, after ligand binding, are transformed into transcription factors modulating gene expression either through DNA binding or through interaction with other transcription factors, e.g. protein–protein interaction (De Kloet et al., 1998). The GR is ubiquitiously distributed over many brain areas with a particularly high concentration in the hippocampus and the hypothalamus. MR expression is much more restricted to the hippocampus, where the MRs are frequently colocalized in cells containing GRs. As mentioned above, corticosteroids vary through a particularly wide concentration range under basal (circadian) conditions, challenge exposure (adaptation to stress), or pathological conditions (depression, inflammation, etc.). To transform this hormonal signal into appropriate cellular responses, a complex response system comprising homodimers between glucocorticoids and mineralocorticoids and, as recently discovered, also through heterodimers, has

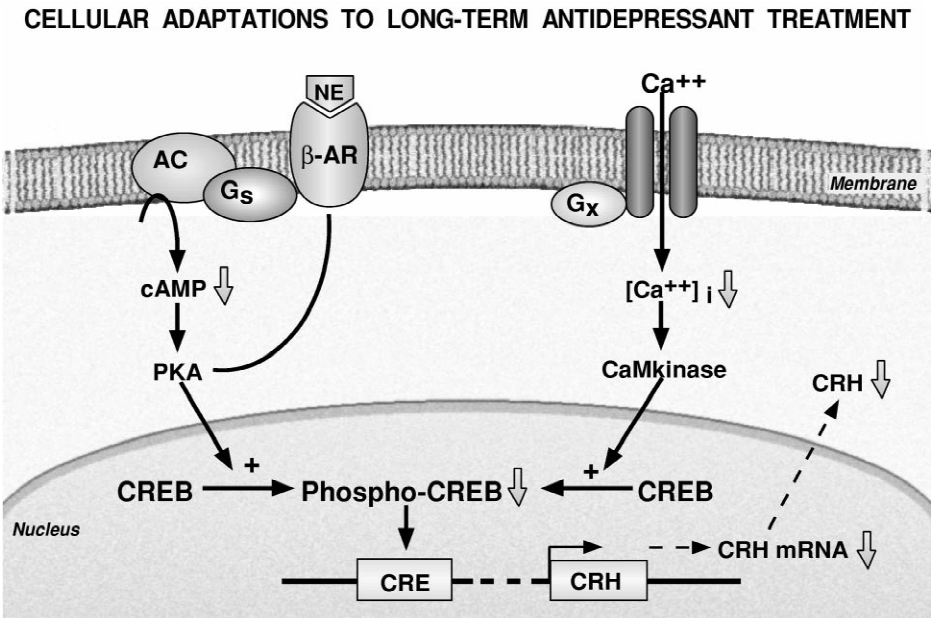

Fig. 11. Postulated effects of antidepressants leading to decreased activation (phosphorylation) of abundant cAMP-response element-binding protein (CREB) and subsequent decrease of CRH gene expression.

been developed (Trapp et al., 1994). The effects of antidepressants on these two receptor systems have been investigated by using two different paradigms, i.e. transgenic mice expressing antisense directed against the mRNA of the GR, and rats whose MR and GR capacity was studied in a time-critical manner in order to define how GRs and MRs respond long-term antidepressant treatment. The studies with transgenic mice used moclobemide, a reversible inhibitor of monoamine oxidase (MAO), which is of advantage for those kinds of studies as it does not interfere with the motor activity of experimental animals. This property is important, because many of the behavioral paradigms used in preclinical antidepressant research are based on emotional and cognitive responses expressed by an avoidance of certain situations (such as entering the open arms of an elevated plus-maze or a lit compartment of a light–dark box, or by the time that elapses until an immobile 'floating' posture is acquired in the forced swim test). Such types of behavior can be confounded by drug-induced changes in motor activity, which may be falsely attributed to changes in emotionality and cognition. When transgenic mice with impaired glucocorticoid receptor function are tested in the forced swim test, they have a much poorer coping strategy than wild-type mice (Montkowski et al., 1995). In addition, their hormonal stress response to this condition is strikingly different. When these mice are chronically treated with moclobemide in a dose range that is equivalent to the clinical situation, they become indistinguishable from wild-type mice in their behavioral response to the forced swim test. Parallel to these changes, their hormonal response to stress tends towards normalcy. These experiments suggest that increased noradrenergic neurotransmission through MAO inhibition corrects the impaired glucocorticoid receptor function on both the behavioral and the neuroendocrine level. This view is supported by a study of Reul et al. (1994), who showed that rats, when treated with moclobemide in a dose range corresponding to clinical dosages, have a reduced hormonal response to stress exposure and that these effects are associated with an increased binding capacity of corticosteroid receptors in the hippocampus. In rats treated with moclobemide and other antidepressants, this group was able to show that these adaptive changes at the level of corticosteroid receptors follow a differential pattern with regard to MR and GR

changes. The initial effect of antidepressants upon corticosteroid receptors was an enhanced MR binding after 2 weeks and an increase in GR binding some weeks later. Translated into the clinical situation, one may expect that full MR function in the hippocampus is required for initiating the adaptive cascade that is triggered by antidepressant drugs. As a clinical proof of this hypothesis, Hundt et al. (unpublished) conducted a study with amitriptyline, a fairly unspecific antidepressant drug that acts on many different neurotransmitter systems. Half of the study sample received amitriptyline and, in addition, spironolactone, an MR antagonist, and the other half received amitriptyline plus a placebo. The rationale of this study was that those patients receiving the MR antagonist are deprived of an appropriate MR function, which is believed to be essential for antidepressant drug response, and should therefore be expected to respond less favorably to the amitriptyline treatment than the patients treated with amitriptyline alone. This was found to be exactly the case, as the results of that double-blind controlled study show.

Altogether, it seems that currently marketed antidepressants act through a large number of intracellular mechanisms downstream the well known cell membrane receptors that bind biogenic amines. Among the adaptive changes induced by long-term antidepressant treatment are changes in transcription factors, such as CREB and GR and MR. While the activation of CREB through phosphorylation is most likely reduced and therefore decreasing the transactivation of the CRH gene, antidepressants also improve the function of corticosteroid receptors. Because suppression of MR function as well as of GR function results in HPA hyperactivity, reinstatement of their full function improves the negative feedback capacity and buffers the HPA system against stress-elicited hyperresponsivity. These two modes of action seem to be complementary as there is a long-term effect of antidepressants upon a number of nuclear transcription factors, including CREB, and the corticosteroid receptors. These adaptive responses may be one explanation for the protracted time of onset of drug action.

However, two questions remain to be addressed in this context: the first is: ‘Would glucocorticoid-receptor antagonists present a worthwhile approach in treating depression associated with HPA overactivity?’ At first glance, such a possibility follows the classical approach in medicine, that is, if a certain compound (in this case cortisol) produced in the body is above the normal range, recuperation from disease or prevention implies that the synthesis of these compounds is inhibited or the receptors through which they act are blocked or only available at reduced levels. However, in the case of hypercortisolemic depression, only a short-term effect of GR antagonists can be anticipated, since, in the long-term, these drugs interfere with the central HPA regulation by activating CRH, vasopressin and other ACTH secretagogues. There may be room for GR antagonists in the treatment of psychotic depression, where hypercortisolism is excessive and believed to pathologically increase the dopaminergic neurotransmission that possibly accounts for the psychotic symptoms.

Studies using metyrapone, a compound that inhibits its hydroxylation at the C_{11}-position of the steroid molecule and thus prevents the biosynthesis of cortisol, are sparse. There is one study, performed by the group of Stewart Checkley in London (O’Dwyer et al., 1995), in which metyrapone was used and the associated loss of cortisol compensated by cortisol coadministration. In this double-blind study in eight patients with depression, metyrapone was found to have some positive antidepressive effects. However, administration of metyrapone leads to the production of a large number of other neuroactive steroids, for example tetrahydrodeoxycorticosterone (THDOC), which have psychotropic effects of their own (Rupprecht and Holsboer, 1999). Patchev et al. (1994) for example, found that THDOC suppresses CRH secretion, which may explain the antidepressive effects of metyrapone.

The second question that needs to be addressed is whether it is possible to shorten the time of onset of antidepressive action by a blockade of central CRH_1 receptors (Fig. 12).

This approach is based on the hypothesis that a CRH hyperdrive accounts for signs and symptoms that are characteristic of depression, and that blocking the CRH_1 receptors would suppress the postulated depressogenic and anxiogenic effects of ex-

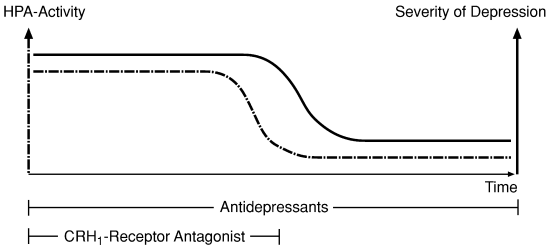

Fig. 12. Antidepressants act through a number of unspecific activations within and between neurons (e.g. phosphorylation of transcription factors), which lead to specific adaptations (e.g. normalization of CRH hyperdrive) that are necessary to resolve the signs and symptoms of depression. It is hypothesized that CRH_1-receptor antagonists, either given alone or as adjunct to antidepressants, may shorten the time until the onset of clinical improvement by blocking CRH-mediated effects at various brain sites involved in the pathogenesis of affective disorders.

cessive CRH secretion (Holsboer, 1999). Here again, the question arises as to whether such a compound would rather be a substitute for the currently available antidepressants or an adjunct. Based on preclinical data, the latter seems to be more likely. Mice with a functional CRH_1-receptor deficit induced through targeted mutagenesis display increased amounts of CRH in those brain areas in which the CRH_1 receptor has been deleted. Translated into the clinical situation, this means that patients treated with CRH_1-receptor antagonists may show an initial positive response, but if they receive the drug for a long time at a high concentration a similar build-up of CRH may be expected and, at the same time, the CRH_1 receptors that are blocked by the antagonist may react overly sensitively because of the antagonist-induced upregulation. Provided that this is also the case in the clinical condition, cessation of drug treatment would theoretically trigger a relapse, because an increased number of ligands are able to convey the signal through an increased (upregulated) number of CRH_1 receptors. However, considering the evidence that has emerged from the preclinical and clinical studies performed so far, it seems plausible that CRH_1-receptor antagonists are a most promising tool when they are given as an adjunct to antidepressant treatment. Furthermore, clinical studies are needed to test whether they might even turn out to be effective as an antidepressant monotherapy.

There is also another aspect that favours the concept of an important role of CRH_1-receptor antagonists in all conditions in which excessive central CRH activity is causally involved in pathology. Blockade of CRH_1 receptors seems to work only in cases in which CRH is hypersecreted in certain brain areas. Basal neuroendocrine activity is not influenced by the absense of a CRH_1 receptor, as it has been shown in mouse mutants lacking this particular receptor subtype (Timpl et al., 1998; Smith et al., 1998). Under basal conditions the HPA system functions well, even in the absence of CRH_1 receptors. This is also true in humans in whom CRH_1-receptor antagonism does not induce any kind of addisonian (hypocortisolemic) symptomatology (Zobel et al., 2001). Thus, unlike benzodiazepines by which irrespective of the individual set-point sedation is induced, CRH_1-receptor antagonists promise to work only under conditions of elevated stress. Therefore, as shown in mice with a CRH_1-receptor knockout, an indication for an administration of CRH_1-receptor antagonists can be predicted for a large number of different conditions, including alcohol withdrawal, sleep disorders, anorexia, central inflammatory diseases (e.g. multiple sclerosis), posttraumatic stress disorder, and ischemic insults following stroke. It also seems fair to say that these drugs may have a potential for misuse, for example in tempting individuals to prepare themselves for coping with anxiogenic or extreme stress situations, thus rendering them less responsive with regard to their adequate, immediate self-protective reflexes. Moreover, it should be stressed that blocking central CRH receptors is a psychopharmacological principle that may not only be limited to patients who show an HPA overactivity. In other words, those patients with depression in whom the traditional methods of HPA activity assessment do not reveal any signs of pathology are not necessarily potential nonresponders to CRH_1-receptor antagonists. Likewise, patients with normal peripheral signs of HPA activity may as well have an essential disturbance of CRH receptor-mediated neurotransmission as a major underlying cause of psychopathology. Therefore, HPA measurements will more likely present a helpful tool

in assessing the potentially effective dosage, with patients showing higher HPA activity requiring higher CRH-receptor antagonist dosages for their response to treatment (Holsboer, 1999).

5. Conclusion

Nearly all drugs that are marketed these days were engineered in analogy to drugs whose antidepressant action was uncovered by a serendipitous finding made by Roland Kuhn in Switzerland some 40 years ago. This is interesting as there has never been any compelling evidence that patients do have an actual deficit in central serotonin or norepinephrine or other neurotransmitter function. Considering the diverse action of these drugs on biogenic amine-mediated neurotransmission, they have a surprisingly uniform clinical profile. On the neurobiological level they have one property in common: if they work successfully, this positive effect is associated with a normalization of an initially hyperactive HPA system. Alteration of this neuroendocrine system has been shown to be a very frequent concomitant in a large variety of psychiatric conditions, foremost depression. With the help of behavioral and molecular pharmacology and gene technology, all clinical and preclinical data were found to be consistent with the view that HPA hyperactivity is causally linked to depression and to the modes of action of antidepressants. Because CRH was found to be the driving force in this cascade, elaboration of the clinical profile of drugs that antagonize its actions seems to be worthwhile. It is noteworthy, however, that such clinical validation of a neuroendocrine concept must liberate itself from the boundaries of nosological entities. It seems much more appropriate to look into the condition of HPA hyperactivity across all clinical conditions in which such neuroendocrine signs and symptoms are prevalent, and then to build up the differential therapies focused on these neurobiological abnormalities. The near future will bring about a further denosologization of psychiatric treatments. As individual patients are polymorphic, just as diseases are, an individual genotyping and documenting of time-dependent changes of gene expression patterns following pharmacotherapeutic intervention will allow — with much more precision than it has ever been thought to be possible — for a ‘customized’ choice of drugs, duration of treatment and dosage.

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