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Review

Central CRH system in depression and anxiety — Evidence from clinical studies with CRH_1 receptor antagonists

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Abstract

Basic and clinical studies provide convincing evidence that altered stress hormone regulation frequently observed in depression and anxiety are caused by elevated secretion of the hypothalamic neuropeptides corticotrophin releasing hormone (CRH) and vasopressin. CRH predominantly acts through CRH_1 receptors to produce a number of anxiety- and depression-like symptoms, which resulted in extensive validation of CRH_1 receptors as potential drug target. A number of orally available nonpeptidergic small molecules capable to pass the blood-brain barrier have been discovered; only some of these compounds entered clinical development. Here, we summarize results from clinical studies of two CRH_1 receptor antagonists. In the first study originally designed as a safety and tolerability trial in major depression, it was observed that the CRH_1 receptor antagonist NBI-30775/R121919 has a clinical profile comparable to the antidepressant paroxetine. In a second study the effect of another CRH_1 receptor antagonist, NBI-34041, upon stress hormone secretion in response to a psychosocial stressor was investigated. Administration of this compound reduced the stress-elicited secretion of cortisol. Both compounds, however, did not impair the CRH-induced release of ACTH and cortisol rejecting the possibility that the peripheral stress hormone system is impaired by CRH_1 receptor antagonists. From these studies we conclude that both CRH_1 receptor antagonists have psychotropic effects unrelated to their neuroendocrine action, which is in line with behavioral data obtained from transgenic mice. The results of the clinical studies underscore that CRH_1 receptor antagonists represent promising novel therapeutics in the psychopharmacology of depression and anxiety.

Keywords: CRH; CRH_1 receptor antagonists; Depression; Anxiety; Clinical studies

Contents

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1. Introduction

Stress and its neurobiological correlates are substantially involved in causation and development of depression and anxiety disorders. Chronic and acute stressors contribute to disease liability and trigger the onset of these disorders (Heim and Nemeroff, 2001; Charney and Manji, 2004; de Kloet et al., 2005).

In response to any kind of stress the pituitary gland secretes corticotrophin (ACTH), which leads to increased synthesis and release of cortisol (corticosterone in rodents) at the level of the adrenal cortex. Corticotrophin releasing hormone (CRH) and vasopressin are the key central neuropeptides accounting for peripheral increase of stress hormones. Both neuropeptides are synthesized in specialized neurons in the hypothalamus (paraventricular nuclei), from which they reach the anterior pituitary via portal vessels. These neuroendocrine activities are closely associated with a large number of other neural projections resulting in neuropeptide release in many brain areas implicated in the neuroanatomy of depression and anxiety, including the central nucleus amygdala, hippocampus, locus coeruleus and cortical structures, such as the prefrontal cortex.

Both neuropeptides, CRH and vasopressin, are involved in the adaptation of stress as they elicit a number of behavioral responses that are suited to cope optimally with a threat. When hypersecreted over extended periods of time these initially beneficial effects reverse into increased liability for anxiety- and depression-like behavior (Landgraf, 2006). Central administration of CRH to rats or mice as well as CRH overexpression in transgenic mice resulted in behavioral changes including anxiety and depression related symptoms (Britton et al., 1986; Pepin et al., 1992; Stenzel-Poore et al., 1994; Ströhle et al., 1998; Deussing, personal communication).

Many clinical research reports agreed that CRH is elevated in depression, but also in anxiety disorders. For instance, the cerebrospinal fluid of depressed patients contained elevated levels of the CRH (Nemeroff et al., 1984; Landgraf, 2006), which, if extrapolated to the situation in the brain, is consistent with reduced CRH binding in forebrains of depressed suicide victims (Merali et al., 2004; Nemeroff et al., 1988) and elevated numbers of CRH-producing neurons in the paraventricular hypothalamic nucleus of patients with depression (Raadsheer et al., 1994). Elevated CRH was also observed in the cerebrospinal fluid of patients with posttraumatic stress disorders (Bremner et al., 1997). The ACTH response to exogenous CRH was blunted among depressed patients indicating desensitized CRH receptors secondary to central hypersecretion (Gold et al., 1984; Holsboer et al., 1984, 1986). If dexamethasone pretreated patients with depression receive a test dose of CRH, an excessive release of ACTH and cortisol can be observed (Heuser et al., 1994; Ising et al., 2005). Similar results have been described for patients suffering from panic disorder (Erhardt et al., 2006; Schreiber et al., 1996). These findings can be explained by elevated secretion of the hypothalamic neuropeptides CRH and vasopressin, which are negatively regulated by endogenous corticosteroids. As a result, endogenously elevated neuropeptides in combination with exogenously administered CRH amplify each others effects at the level of anterior pituitary to produce excessive ACTH and cortisol secretions.

These findings are major pillars of the corticosteroid receptor hypothesis, submitting that impaired intracellular signaling of steroid-activated hormone receptors (glucocorticoid receptor and mineralocorticosteroid receptor) results in inappropriately high and enduring secretions of both, CRH and vasopressin in the brain and ACTH and cortisol in the periphery (Holsboer, 2000). The latter stress hormone is easily crossing the blood-brain barrier. Because a host of genes expressed in the brain are activated or repressed by corticosteroids, mostly via regulatory response elements, it is not surprising that continuous overexposure of the brain to this stress hormone also produces behavioral changes (McEwen, 2007). These include labile, mostly depressed, mood. Similarly, depressed mood is the most frequent psychopathological change among patients with M. Cushing, characterized by unrestrained hypophyseal-adrenal cortex activity. Another behavioral sequel of hypercortisolism is cognitive deficits, well known to be associated with depression. Many experiments suggested that excessive corticosteroid secretion endangers hippocampal neurons by increasing their vulnerability to noxious agents such as excitatory aminoacids and oxidative stress (Behl et al., 1997; Sapolsky, 2000). A current hypothesis submits that chronic glucocorticoid overexposure increases hippocampal vulnerability, which may render an individual susceptible for pathological stress response, i.e., for the development of a stress-related disorder. Antidepressants probably also work via restoration of this deficit by enhancing hippocampal neurogenesis (Nestler et al., 2002). Some of the depressed patients also show psychotic features. Since hypercortisolism either via a hormone secreting tumor or via corticosteroid medications also often produces psychotic features, it was submitted that the psychotic symptoms are mainly produced by corticosteroid excess (Schatzberg et al., 1985).

As a consequence of these abnormalities induced by various stress hormones their potential role in the pathogenesis of depression has been hypothesized and therefore three complementary lines of pharmacological interventions are currently in the focus of antidepressant drug discovery and development programs (see Fig. 1).

In the following, we focus on the CRH system, discuss CRH receptors as drug targets, and present clinical findings obtained with CRH_1 receptor antagonists.

2. CRH receptors as drug targets

CRH exerts its actions through two different G-protein-coupled receptors (GPGR), CRH_1 and CRH_2 receptors. Both receptors are unequally expressed in the brain, where they not only bind CRH but also three other CRH related peptides: Urocortin I (UCN I), stresscopin-related peptide (also termed UCN II) and stresscopin (UCN III). UCN I binds with equal affinity at both CRH_1 and CRH_2 receptors, while UCN II and III preferentially bind at CRH_2 receptors and have poor affinity for CRH_1 receptors (Grigoriadis, 2005). While both receptor subtypes are co-localized in the human pituitary (Hiroi et al., 2001) and in the neocortex of primates (Sanchez et al., 1999),

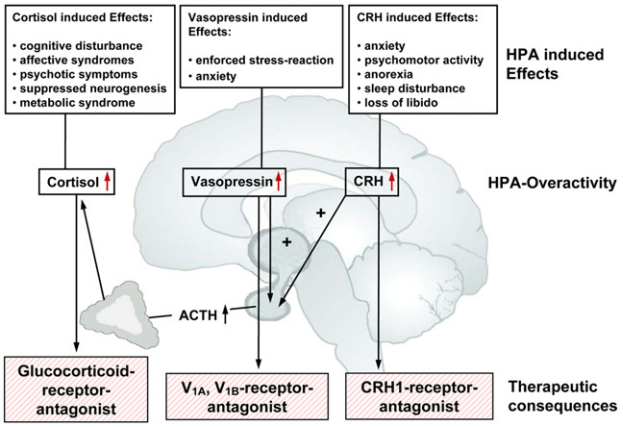

Fig. 1. Activation of the HPA-system results in elevation of CRH, vasopressin, and cortisol, which produce several signs and symptoms of depression and anxiety. Blocking their actions at the receptor level provides a new lead for antidepressant and anxiolytic discovery (Holsboer, in press).

the situation is different in rodents with only CRH_1 receptors expressed in the pituitary and a heterogeneous distribution of both receptors in the neocortex (Chalmers et al., 1995).

As mentioned, a large number of studies using animal models clearly indicated that CRH accounts for many signs and symptoms of depression including a host of stress-related features such as anxiety, sleeplessness, decreased appetite, decreased sexual interest, psychomotor agitation and others. All these findings were derived from studies that either injected CRH into the rodent brain and measured behavioral changes or used mice where CRH was overexpressed in the brain (Heinrichs and Koob, 2004). These behavioral effects of CRH can be targeted by interfering with CRH/CRH_1 receptor signaling as was first shown with peptidergic CRH receptor antagonists [α-helical CRH (9–42), D-Phe-CRH (12–41) and astressin], which all were only poorly selective. Another line of evidence emerged from experiments that used antisense probes directed against CRH_1 receptor mRNA thus preventing translation into receptor proteins (Liebsch et al., 1999). These studies showed that the specific antisense probes not only resulted in reduced CRH but also in decreased stress-elicited anxiety-like behavior. Questions regarding specificity of effects by central peptide injections or antisense probes prompted the generation of mouse mutants where the CRH_1 receptor was deleted by genetic engineering, which confirmed the preeminent role of CRH_1 receptors (Smith et al., 1998; Timpl et al., 1998). The most compelling evidence came from a mouse mutant where CRH_1 receptors were conditionally deleted resulting in a functional CRH_1 receptor depletion that was restricted to the limbic system (Müller et al., 2003). This finding was important, because in mutants where CRH_1 receptors are also nonfunctional in the periphery – primarily the pituitary – the abnormal stress hormone regulation had to be considered as potential confounder as these hormones also elicit behavioral changes (Müller and Holsboer, 2006). This mouse model confirmed that CRH_1 receptors in the brain are responsible for anxiety-like behavior and supported the hypothesis submitting that antagonism of CRH_1 receptor activity may provide a novel hypothesis-driven pharmacological strategy for treatment of stress-related disorders such as depression and anxiety (Holsboer, 1999).

A number of nonpeptidergic small molecules with good oral bioavailability and rapid penetration across the blood-brain barrier were developed and tested in preclinical models of depression and anxiety. The inconsistencies of some of the test results can be ascribed to the fact that the animal models used were validated for the discovery of antidepressants acting at monoamine transmitter reuptake transporters (Markou, 2005). This is exemplified by the recent observation that a mouse that overexpresses CRH conditionally in the brain displays hyperactivity when exposed to the forced swim test (Lu, personal communication), as these mice exhibit enhanced struggling and reduced floating times. When treated with DMP 696, a selective CRH_1 receptor antagonist, struggling time decreased while floating increased. This observation is in opposition to the behavioral changes observed in wild-type mice, where mice and rats, when treated with antidepressants, exhibit decreases in floating relative to struggling (Markou, 2005). In wild-type mice, where depression or anxiety-like behavior is absent, most CRH_1 receptor antagonists reduced immobility in a similar way as observed after administration of monoamine-based antidepressants. The relevance of the affective state at baseline, which is now deemed as pertinent for interpretation of drug effects on a stress-related behavior is demonstrated in rat and mouse lines which have been selectively and bidirectionally bred for extremes in trait anxiety. As a result rats and mice with high innate anxiety-like behavior assessed on the elevated plus-maze became available (Wigger et al., 2004). Rats (Keck et al., 2001) and mice (Bunck, personal communication) with high innate anxiety-like behavior but not rodents with innate low anxiety responded to the CRH_1 receptor antagonists NBI-30775/RS1 21919 and DMP 696, respectively. These findings emphasize the importance of emotional states of experimental animals prior to screening of drugs with potential psychotropic properties.

For almost 20 years a large number of small molecule CRH_1 receptor antagonists have been discovered, but only few of them entered clinical development and still none of them found its way to the market (Valdez, 2006). While still a number of clinical trials are under way, results have been published so far only for two compounds, NBI-30775/RS121919 (compound 2; 2,5-dimethyl-3-(6-dimethylamino-4-methylpyridin-3-yl)-7-dipropylaminopyrazolo[1,5-a]pyrimidine) and NBI-34041 (compound 12t; 2-(2,4-dichlorophenyl)-4-methyl-6-(1-propyl-butyl)-7,8dihydro-6H-1,3,6,8a-tetraazaacenaphthylene), both initially developed by Neurocrine Biosciences, San Diego, USA (Gross et al., 2005).

3. CRH_1 receptor antagonists in clinical trials

3.1. Open-label dose-escalation trial with NBI-30775/R121919

The first clinical study published was an open-label trial designed to assess the safety of NBI-30775/R121919. This drug is a nonpeptide tricyclic high-affinity CRH_1 receptor antagonist, which is well absorbed when given orally, penetrates the blood-brain barrier and binds specifically to cloned human CRH_1

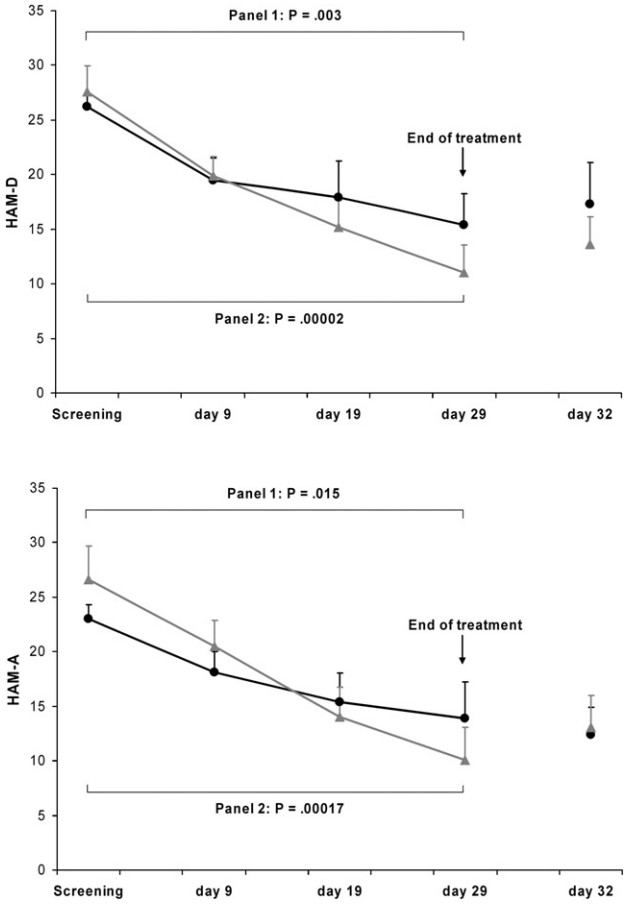

Fig. 2. Change in HAM-D (depression) and HAM-A (anxiety) rating scale scores after 5 to 40 mg/day (black lines, circles) and 40 to 80 mg/day (gray lines, triangles) NBI-30775/R121919 treatment (Zobel et al., 2000).

receptors with high-affinity (Ki=3.5 nmol/L), while binding to other neurotransmitter and neuropeptide receptors or transporters is absent or more than 1000-fold lower (Chen et al., 2004; Heinrichs et al., 2002; Steckler and Dautzenberg, 2006). Oral administration in rats led to anxiolytic-like effects in different test paradigms and antagonized behavioural effects induced by CRH pretreatment (Heinrichs et al., 2002). In rats selectively bred for high anxiety-like behaviour the CRH_1 receptor antagonist NBI-30775/R121919 blocked CRH binding to CRH_1 receptors and exerted anxiolytic effects in a dose-dependent manner in these rats (Keck et al., 2001). Comparable anxiolytic effects of NBI-30775/R121919 were absent in rats that were selectively bred for low anxiety.

An open-label phase IIa clinical trial examining the effects of increasing doses of NBI-30775/R121919 in depressed patients was conducted a the Max-Planck-Institute of Psychiatry in Munich (Held et al., 2004; Künzel et al., 2003; Zobel et al., 2000). The study population (n=20) was split into equally sized groups that received during 30 days either a dosage escalating from 5 to 40 mg/day or from 40 to 80 mg/day. After 30 days, treatment was discontinued for two days, before treatment with classical antidepressants was commenced. The clinical evaluation was designed as open-label trial in order to study safety and tolerability. Additionally, changes in psychopathology scores, laboratory examinations and change in sleep performance including polysomnography were independently recorded.

The patient group receiving higher dosages showed better improvement (see Fig. 2) including distinct reduction of depression as well as anxiety symptoms. In fact, in the higher dose panel eight out of ten patients met the criterion of treatment response (i.e. a reduction of the score at baseline of at least 50% on the 21 items Hamilton Rating Scale for Depression, HAM-D; Hamilton, 1996) and six out of ten patients were classified as being remitted (HAM-D score of less or equal 8 points at the end of the study). In the low dose panel only five patients were responders, while three of them achieved remission. Conclusions based on a small open-label trial are limited. Nevertheless the effect size of the higher dose panel after a treatment period of 29 days was compared with that of paroxetine, collected from a double-blind randomized clinical trial over the same observation period (Nickel et al., 2003). Both studies were conducted with depressed inpatients from the same hospital applying comparable inclusion criteria and a similar study procedure. As illustrated in Fig. 3, the effect sizes of both drugs regarding the HAM-D total score, the HAM-D subscales Vegetative and Cognitive Depression (Rhoades and Overall, 1983), as well as suicidality are well comparable. No significant differences could be observed (P>.235) suggesting similar efficacy and a comparable profile of action between NBI-307 75/R121919 and paroxetine.

Examinations including clinical chemistry and hematology, electroencephalography and electrocardiography failed to show any adverse effects regardless of dosage of NBI-30775/R12 1919 (Künzel et al., 2003). An in depth hormonal evaluation analyzing all endocrine systems also confirmed the safety of the drug. That includes that the pituitary–adrenocortical response to an intravenously administered test dose of 100 μg human CRH was not affected by the drug (Zobel et al., 2000). This is of importance because it confirms that even if a dose is administered that blocks effectively central CRH_1 receptors, there are still sufficient receptors available at the anterior pituitary corticotrophs that can be stimulated by CRH. Thus, the stress

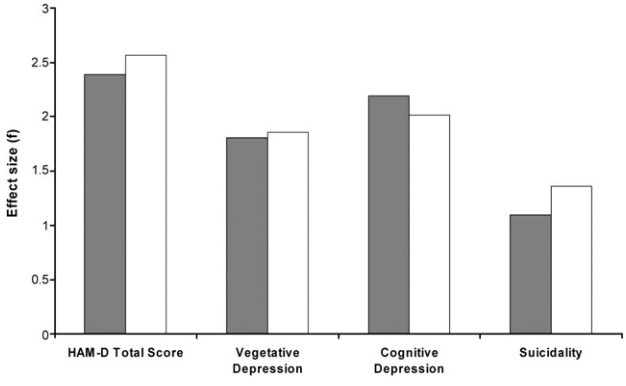

Fig. 3. Effects sizes f of the HAM-D total score, HAM-D subscales of Vegetative and Cognitive Depression, and Suicidality evaluated with items from the HAM-D, the Montogomery-Asberg-Depression Rating Scale, and the Beck Depression Inventory after four weeks of treatment with 20 to 40 mg/day paroxetine (gray columns) and 40 to 80 mg/day NBI-30775/R121919 (white columns) (Ising and Holsboer, 2007).

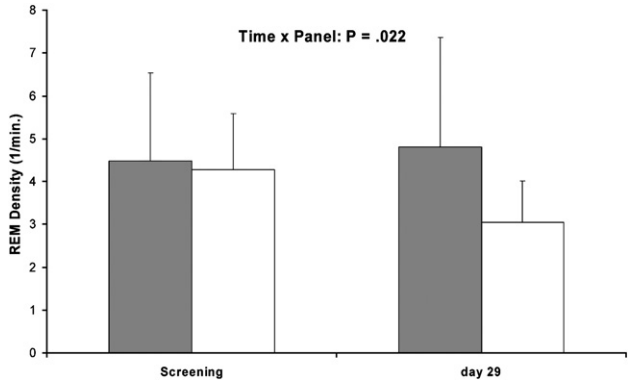

Fig. 4. REM-density before and after 29 days of 5 to 40 mg/day (gray columns) and 40 to 80 mg/day (white columns) NBI-30775/R121919 treatment (Held et al., 2004).

hormone system responsivity to CRH remains unchanged, which is of importance, because patients treated with such a drug need to maintain their capacity to respond adequately to stressors, e.g., to an infection.

Disturbed sleep is a cardinal symptom of depression. Polysomnographic studies showed that patients with depression have shortened REM-latency, increased REM-density and decreased slow-wave sleep. The latter feature is reported to be induced by CRH in both animals and humans (Steiger, 2007). A sleep-EEG analysis in a random subgroup of patients treated with NBI-30775/R121919 revealed that this treatment increased slow-wave sleep and decreased REM-density (Held et al., 2004). As illustrated in Fig. 4, the latter effect was only observable among patients receiving the higher dose of NBI-30775/R121919. Despite these very promising clinical results the further development was discontinued because of liver enzyme elevation observed in two healthy subjects after administration of much higher dosages than believed to be necessary to occupy all available CRH_1 receptors in the brain. These abnormalities were reversible and not related to the pharmacological mechanism of the drug, because CRH_1 receptors are absent in liver tissue.

3.2. Randomized placebo-controlled proof of concept study with NBI-34041

Another CRH_1 receptor antagonist, the nonpeptide tricyclic NBI-34041 developed by Neurocrine Biosciences was recently clinically investigated. This compound can also be orally administered, passes the blood-brain barrier and binds to CRH_1 with high (Ki=4.0 nmol/L) affinity. The drug was given to 24 healthy male volunteers in the format of a randomized double-blind placebo-controlled study where three different dosages (10, 50 and 100 mg/day) were administered over a time period of 14 days. The study was designed to evaluate whether subchronic treatment with the investigational drug would decrease the stress hormone response following a psychosocial stressor (Ising et al., 2007b). For that purpose the Trier Social Stress Test (TSST) was applied after nine days of treatment with NBI-34041 or placebo. The TSST is a standardized public speaking procedure, involving a mock job interview and mental arithmetics (Kirschbaum et al., 1993; Zimmermann et al., 2004). During and following the test paradigm plasma ACTH and cortisol concentration time course curves were monitored. All subjects responded to the psychosocial stressor with moderate tension or vigor, which is an important prerequisite for achieving optimal performance (Dickman, 2002). However, as illustrated in Fig. 5, plasma ACTH and cortisol response was attenuated when the study participants were pretreated with the high dose of NBI-34041. As already observed with NBI-30775/R121919, none of the drug dosages used prompted a decreased release of plasma ACTH and cortisol in response to an intravenously administered test dose of CRH. In addition, no systematic effects of NBI-34041 treatment on basal ACTH and cortisol plasma levels, urinary free cortisol concentrations or on

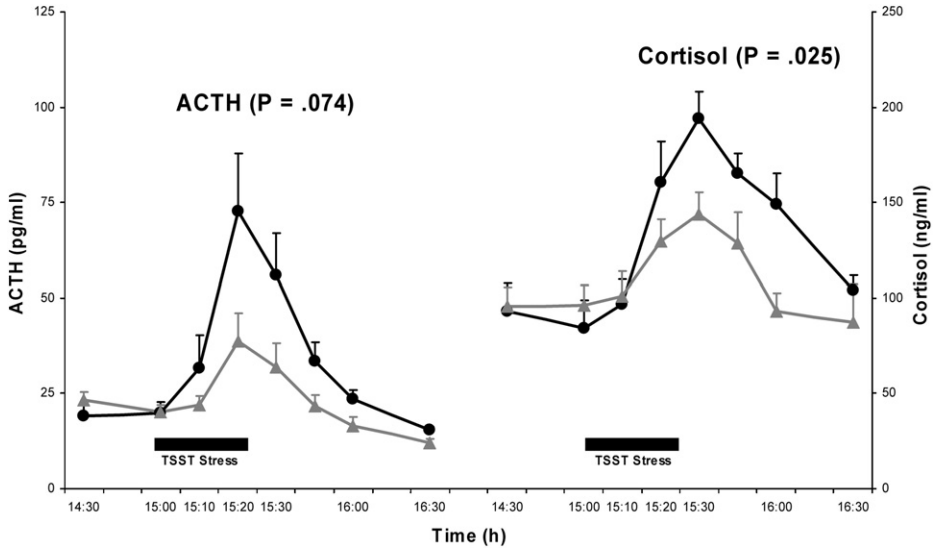

Fig. 5. ACTH (left part) and cortisol response (right part) to a standardized psychosocial stress test (Trier Social Stress Test) after 9 days of treatment with 100 mg/day NBI-34041 (grey lines) or placebo (black lines) (Ising and Holsboer, 2007).

circadian ACTH and cortisol secretion were observed, confirming that treatment with NBI-34041 was safe in all dose-groups (Ising et al., 2007b).

3.3. The CRH_1 receptor antagonist pipeline

Several drug companies are currently developing CRH_1 receptor antagonists. Neurocrine Biosciences, who have discovered and developed NBI-30775/R121919, NBI-34041 and several other compounds (Chen et al., 2004), continue with their CRH receptor program in partnership with GlaxoSmithKline (GSK). According to the Neurocrine Biosciences internet webpage, phase I double-blind placebo-controlled trials are ongoing and GSK is planning to initiate phase II trials in anxiety/depression during 2006 (http://www.neurocrine.com/html/clin_anxietyDepression.html).

Bristol-Myers Squibb announced in their 2006 annual report (http://www.bms.com/annual/2006ar/msite/data/bms_ar_06.pdf), that a CRH receptor antagonist for treating depression is in early clinical development.

Taisho Pharmaceuticals report about a CRH_1 receptor antagonist for depression and anxiety disorders in their 2006 annual report that has been developed in collaboration with Janssen Pharmaceutica and is currently in the phase 1 stage of development (http://www.taisho.co.jp/ir/annual/report/pdf/06_all.pdf).

Other international pharmaceutical companies including Novartis, Pfizer, and Sanofi-Aventis have CRH_1 receptor antagonists in their drug pipelines (Steckler and Dautzenberg, 2006), but it is yet not made public, which of these candidates is still in clinical development and which is not.

4. Conclusion and future directions

The huge basic science data base contrasts with the paucity of clinical reports using CRH_1 receptor antagonists. In fact, a number of unreported clinical trials were discontinued because of toxic side effects. Importantly, these adversities do not question the pharmacological principle of muting CRH/CRH_1 receptor signaling, as toxicity of investigational CRH_1 receptor antagonists was observed in tissues not carrying CRH_1 receptors. Once a CRH_1 receptor antagonist has taken all the hurdles needed to enter the market it remains undecided what their ultimate role in clinical practice will be. To establish a clinical differentiation against current antidepressants or new drugs that act at different pathways at least three imminent questions need to be addressed: (1) which clinical symptoms are sensitive to treatment with CRH_1 receptor antagonists?; (2) are CRH_1 receptor antagonists acting preferentially among patients with documented hyperactivity of the hypothalamic-pituitary-adrenocortical stress hormone axis; and (3) are CRH_1 receptor antagonists alternative treatments to current antidepressants or adjuncts to improve time to onset of action and remission rate?

For giving a profound answer to the first question, more clinical studies with symptomatic subjects or patients are required. Considering the results of the animal studies and taking the primary mode of action into account, one could speculate that CRH_1 receptor antagonists primarily attenuate anxiety related symptoms and might be less efficient in reducing symptoms of cognitive depression. However, the results of the dose-escalation trial with NBI-30775/R121919 suggest that this is not the case. NBI-30775/R121919 was efficacious in reducing anxiety related symptoms and sleep disturbances (HAM-D subscale Vegetative Depression), improved depressed mood, drive, and cognitive symptoms (HAM-D subscale Cognitive Depression) and reduced suicidality (see Fig. 3). These effects were well comparable with the effects of the antidepressant paroxetine, which is an established selective serotonin reuptake inhibitor. Regarding the second question the available data – though limited – suggest that current neuroendocrine HPA tests only poorly predicted CRH_1 receptor antagonist treatment outcome (Zobel et al., 2000). In fact, results from both, transgenic mice carrying CRH_1 receptor gene deletions or from depressed patients undergoing HPA tests suggest that disturbed central CRH/CRH_1 receptor signaling is not necessarily reflected by peripheral pituitary-adrenocortical measures (Müller et al., 2003). Ideally, positron emission tomography (PET), allowing to quantify central CRH_1 receptors with a PET-active CRH-ligand could serve as a biomarker to identify patients which would benefit from such a treatment. A different approach was chosen in pharmacogenetic studies, where an association of a CRH_1 receptor gene haplotype and antidepressant treatment response was found. However, the prediction was limited to patients with high anxiety scores (Licinio et al., 2004; Liu et al., 2007), which is in line with many basic studies indicating that central CRH overexposure by pharmaceuticals or transgenesis elicit anxiety-like behavior.

The possibility, that CRH_1 receptor antagonists might be well suited adjunctive treatment is supported by a huge number of studies showing that the normalization of initially disturbed HPA-axis activity is under almost all antidepressant treatments preceding the resolution of depressive symptoms (Ising et al., 2007a). It may be worth testing if a combination of a current antidepressant and a CRH_1 receptor antagonist offers an advantage over a treatment with one or the other modality. This approach may result in a hastened onset of antidepressant action.

The results of the proof of concept study with NBI-34041 suggest that this CRH_1 receptor antagonist was capable in reducing the stress hormone secretion in response to a demanding psychosocial stress situation. This has obvious implications for understanding causality and – more specifically – onset of depression, because stress exposure is an important trigger for the development of depression in predisposed individuals (Paykel, 2003). According to the corticosteroid receptor hypothesis of depression the signaling capacity of mineralo- and glucocorticoid receptors is impaired in this disorder (Holsboer, 2000). As a consequence of an impaired mineralocorticoid receptor function the threshold at the onset of the stress response is lowered and signaling via CRH/CRH_1 receptor pathways is facilitated. The peripheral stress hormone response is functionally dominated by enhanced plasma cortisol concentration, which exerts a negative feedback via glucocorticoid receptors. If glucocorticoid receptor function is impaired, the CRH/CRH_1

receptor signaling remains insufficiently curtailed resulting in a number of failed adaptations and finally in development of disease (de Kloet et al., 2005). Based on these mechanisms and the herein reported study results with NBI-34041, it seems worthwhile considering testing this and other CRH_1 receptor antagonists as treatment to prevent development of stress-related disorders such as depression, anxiety, and posttraumatic stress disorder among those having experienced a severe trauma.

Whatever the final indication might be, prevention of stress-related disease following trauma, combination with antidepressants to accelerate onset of action or monotherapy — there is little doubt that CRH_1 receptor antagonists represent promising novel therapeutics in the psychopharmacology of depression and anxiety.

Conflict of interest statement

Florian Holsboer, MD, PhD, is founder and shareholder of Affectis Pharmaceuticals, and shareholder of Corcept and Neurocrine Biosciences. Marcus Ising, PhD, has nothing to disclose.

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