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CRH_1 Receptor Antagonists for the Treatment of Depression and Anxiety

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From basic and clinical studies, ample evidence has emerged that abnormalities of stress hormone regulation observed in depression and anxiety are caused by elevated secretion of hypothalamic corticotropin-releasing hormone (CRH). This neuropeptide acts through CRH_1 receptors to produce a number of anxiety- and depression-like symptoms, which has resulted in extensive validation of CRH_1 receptors as a potential drug target. A number of orally available nonpeptidergic small molecules that are able to pass the blood–brain barrier have been discovered. Some of these compounds have entered clinical development. The authors summarize results from clinical studies of 2 CRH_1 antagonists. One study designed as a safety and tolerability study also monitored amelioration of depression under 2 dose-escalation regimens. The compound studied, NBI-30775/R121919, was found to have a clinical profile comparable to that of paroxetine. In a second study the effect of another CRH_1 antagonist, NBI-34041, on stress hormone secretion in response to a psychosocial stressor was investigated. Administration of this compound to healthy controls was found to reduce the stress-elicited secretion of stress hormones. However, neither compound impaired the CRH-induced release of adrenocorticotropic hormone and cortisol, rejecting the possibility that the stress hormone system is impaired by CRH_1 antagonists. From these studies the authors conclude that both CRH_1 antagonists have psychotropic effects unrelated to their neuroendocrine action, in line with behavioral data obtained from transgenic mice with CRH_1 gene deletions. The psychotropic effects observed in the clinical studies underscore that CRH_1 antagonists constitute a novel treatment of depression and anxiety but may also serve to prevent negative sequelae of severe stressors.

Keywords: depression, anxiety disorders, HPA axis, CRH, CRH_1 antagonist

Depression and anxiety disorders are by far the most frequent psychiatric diseases, with lifetime prevalence rates in Europe and the United States close to 20% for depressive disorders (Jacobi et al., 2004; Kessler et al., 1994) and between 20% (Bijl, Ravelli, & van Zesser, 1998) and 25% (Kessler et al., 1994) for anxiety disorders. The majority of these cases are in need of antidepressant treatment. Depressive disorders are currently categorized as unipolar major depression (single or recurrent episodes), bipolar disorder, or chronic depression. Anxiety disorders include general anxiety disorder, panic disorder, phobic disorders (specific phobias, agoraphobia, social phobia), and posttraumatic stress disorder, with obsessive–compulsive disorders also frequently assigned as anxiety disorders.

A large number of antidepressant drugs are currently on the market, and all of them are used to treat depression and anxiety. The majority of these drugs act by enhancing central monoaminergic neurotransmission, mostly by inhibiting presynaptic reuptake transporters. Mood stabilizers modulating serotonergic, noradrenergic, GABAergic, or glutamatergic neurotransmission are additionally available for recurrent depression, treatment-resistant depression, and bipolar disorder.

Treatment efficacy of currently available antidepressants is acceptable, as most studies report response (i.e., improvement of more than 50%) in about 60%–70% of patients, with full remission (i.e., near absence of residual depressive symptoms) being achieved in about half of patients. In a large, multicenter outpatient study of major depression, treatment with a typical antidepressant, a selective serotonin reuptake inhibitor, was successful in terms of achieving full remission in only 27.5% of the patients, although treatment was applied up to 14 weeks (Trivedi et al., 2006). After nonresponding patients switched to another class of antidepressants, remission was accomplished in only 18%–25% of additional patients (Rush et al., 2006). Although this study has many drawbacks, it sheds some light on the current situation under naturalistic conditions. It is fair to say that the antidepressants currently available work in too few patients and have too many side effects. Also, the protracted onset of action is a serious disadvantage, particularly in the light of increased risk for suicide after treatment initiation. Anxiolytic drugs, including benzodiazepines, are highly effective in ameliorating acute anxiety in a quick and sustained manner. However, these drugs are not suitable for medium- or long-term treatment owing to their high risk for dependence and the increasing likelihood of severe with-

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drawal symptoms after discontinuation (O'Brien, 2005; Salzman, 1998; Stevens & Pollack, 2005).

These limitations of current antidepressant and anxiolytic medications have fueled the discovery of new drug targets and treatment options in depression and anxiety disorders. A number of compounds not primarily acting on monoamine neurotransmission are currently under development, including neurokinin 1 receptor antagonists, *N*-methyl-D-aspartate receptor antagonists, vasopressin receptor antagonists, glucocorticoid receptor antagonists, and corticotropin releasing hormone (CRH; or corticotropin-releasing factor, CRF) antagonists. Focusing on CRH antagonists, we summarize the rationale and clinical data of these compounds and then discuss their suitability as new treatment options for depression and anxiety disorders.

Elevated CRH in Depression and Anxiety Disorders

Stress and its neurobiological correlates are substantially involved in the causation and development of depression and anxiety disorders. Encumbering, chronic stressors contribute to disease liability of affective diseases, and traumatic, acute stressors trigger the onset of these disorders (Charney & Manji, 2004; Heim & Nemeroff, 2001; Paykel, 2003). Impaired regulation of the hypothalamus–pituitary–adrenocortical (HPA) system, which is the major constituent of the neuroendocrine response to acute and chronic stress, is the most consistent laboratory finding in depression (for reviews, see Holsboer, 2000; Ising et al., 2005; Pariante & Miller, 2001; Raison & Miller, 2003). Altered regulation of the HPA system can also be observed in panic disorders (Erhardt et al., 2006; Schreiber, Lauer, Krumrey, Holsboer, & Krieg, 1996) and posttraumatic stress disorder (de Kloet et al., 2006; Duval et al., 2004; Golier, Schmeidler, Legge, & Yehuda, 2006; Griffin, Resick, & Yehuda, 2005; Yehuda, Golier, Halligan, Meaney, & Bierer, 2004), both characterized by sudden attacks of intense fear and pronounced avoidance behavior.

CRH is a 41-amino-acid neuropeptide, discovered by Vale, Spiess, Rivier, and Rivier (1981), that is widely expressed throughout the central nervous system and in several peripheral tissues. In the brain, CRH is concentrated in the hypothalamic paraventricular nucleus (PVN) but also localized in the limbic system and prefrontal cortex (for a review, see S. M. Smith & Vale, 2006), and it acts as a key player in the coordination of neuroendocrine, autonomic, and behavioral responses to stress (for reviews, see Heinrichs & Koob, 2004; Steckler & Holsboer, 1999). It is released from parvocellular neurons of the PVN into the portal vessel system to activate the synthesis and release of corticotropin (ACTH) from the anterior pituitary. ACTH, in turn, stimulates the adrenal cortex to synthesize and release glucocorticoids, in particular cortisol, in humans. These hormones have manifold functions essential for the adaptation to acute stress but can be pathogenic when the organism is persistently exposed. This effect has been demonstrated by a large number of preclinical studies. Central administration of CRH in rats or mice as well as CRH overexpression in transgenic mice resulted in behavioral changes including anxiety and depression-related symptoms (Britton, Lee, Dana, Risch, & Koob, 1986; Pepin, Pothier, & Barden, 1992; Stenzel-Poore, Heinrichs, Rivest, Koob, & Vale, 1994; Ströhle, Poettig, Barden, Holsboer, & Montkowski, 1998).

In accordance with these findings, clinical studies suggest that elevated levels of CRH are present in patients during acute depression. For instance, the cerebrospinal fluid of depressed patients contained elevated levels of CRH (Nemeroff et al., 1984), 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, Owens, Bissette, Andorn, & Stanley, 1988) and elevated numbers of CRH-producing neurons in the PVN of patients with depression (Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994). Furthermore, the ACTH response to exogenous CRH was blunted among depressed patients, indicating desensitized CRH receptors secondary to central hypersecretion (Gold et al., 1984; Holsboer, von Bardeleben, Gerken, Stalla, & Muller, 1984). After successful antidepressant treatment, elevated CRH levels seem to normalize (Heuser et al., 1998), which has also been shown for cerebrospinal fluid CRH levels after electroconvulsive therapy (Nemeroff, Bissette, Akil, & Fink, 1991). These results, together with a plethora of other clinical and preclinical findings, demonstrate that CRH is hypersecreted in depression and possibly also in anxiety, at least as far as the preclinical findings are considered and when the broad overlap between symptoms of anxiety and depression is taken into account. Accordingly, the CRH system has been suggested as a promising target for potentially antidepressant or anxiolytic compounds.

CRH Receptors as Drug Targets

CRH acts at two types of G-protein-coupled receptors belonging to the Class B family (Arzt & Holsboer, 2006), CRH_1 and CRH_2, with CRH_2 existing in three identified splice variants, named $CRH_{2(a)}$, $CRH_{2(b)}$, and $CRH_{2(c)}$ (Hauger et al., 2003). Although both receptor subtypes are colocalized in the human pituitary (Hiroi et al., 2001) and in the neocortex of primates (Sanchez, Young, Plotsky, & Insel, 1999), 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, Lovenberg, & De Souza, 1995). In addition to CRH, another family of endogenous ligands, so-called urocortins, activates these receptors. Urocortin 1 has equal affinity for both receptor subtypes, whereas Urocortins 2 and 3 are selective for the CRH_2 receptor subtype (Perrin & Vale, 1999; Skelton, Owens, & Nemeroff, 2000).

The observation of elevated levels of CRH during acute depression, the anxiogenic effects of central CRH in animal models, and the fact that human CRH binds at the CRH_1 receptor with 15-fold higher affinity over the CRH_2 led to the hypothesis of selective CRH_1 receptor antagonists as appropriate drug targets for the treatment of depression and anxiety. This hypothesis has been confirmed by studies with mouse mutants lacking CRH_1 receptors, which showed less

stress-induced anxiety-like behavior compared with wild-type animals (Müller et al., 2003; G. W. Smith et al., 1998; Steckler & Dautzenberg, 2006; Timpl et al., 1998).

Since 1991, a large number of small molecule CRH_1 antagonists have been developed (Gross et al., 2005; McCarthy, Heinrichs, & Grigoriadis, 1999; Saunders & Williams, 2003; Steckler & Dautzenberg, 2006; Valdez, 2006; Zorrilla & Koob, 2004). However, only a small number of these compounds entered clinical development, and clinical data have been published so far for only two compounds, NBI-30775/RS121919 (Compound 2) and NBI-34041 (Compound 12t), both initially developed by Neurocrine Biosciences, in San Diego, California (Gross et al., 2005).

Clinical Trials With NBI-30775/RS121919 and NBI-34041

Two clinical trials with CRH_1 receptor antagonists have been published so far, one open-label Phase IIa trial in depressed patients (NBI-30775/RS121919) and one randomized double-blind placebo-controlled Phase I proof-of-concept study in healthy male subjects (NBI-34041).

Open-Label Dose-Escalation Trial With NBI-30775/R121919

NBI-30775/R121919 is a nonpeptide tricyclic high-affinity CRH_1 antagonist. It is well absorbed when given orally, and it penetrates the blood–brain barrier and binds specifically to cloned human CRH_1 receptors with high affinity (Ki = 3.5 nmol/L), while binding to other neurotransmitter and neuropeptide receptors or transporters is absent or more than 1,000-fold lower than for the respective ligand (Chen et al., 2004; Heinrichs, De Souza, Schulteis, Lapsansky, & Grigoriadis, 2002; Steckler & Dautzenberg, 2006). Oral administration in rats led to anxiolytic-like behavioral actions in different test paradigms and antagonized behavioral effects induced by CRH pretreatment (Heinrichs et al., 2002). In rats selectively bred for high anxiety-like behavior, 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 at the Max-Planck-Institute of Psychiatry in Munich, Germany (Held et al., 2004; Kunzel et al., 2003, 2005; Zobel et al., 2000). A total of 24 drug-free inpatients suffering from major depression participated, of whom 20 completed the trial. The first 10 patients (the low-dose panel) were treated with 5 mg/day NBI-30775/R121919 for the first 10 days, 20 mg/day for the next 10 days, and 40 mg/day for a further 10 days. After 30 days, treatment was discontinued for 2 days, at which point treatment with classical antidepressants was commenced. The other 10 patients (the high-dose panel) started with 40 mg/day NBI-30775/R121919, which was increased to 60 mg/day after 10 days and then to 80 mg/day after another 10 days. The main purpose of this study was to test whether NBI-30775/R121919 is safe and well tolerated. However, psychopathology was comprehensively recorded during the trial, allowing an assessment of the treatment effects.

As illustrated in Figure 1, depression symptoms rated by the study clinicians (Hamilton Rating Scale for Depression; HAM–D; Hamilton, 1996b) as well as by the patients (Beck Depression Inventory; BDI; Beck, Rush, Shaw, & Emery, 1986) dropped distinctly in patients of the high-dose panel, who were treated with 40 to 80 mg/day NBI-30775/R121919 for 30 days. In the low-dose panel (5 to 40 mg/day NBI-30775/R121919), HAM–D improvement was less pronounced but still significant, whereas change in the patients' BDI ratings did not reach significance. Even though both panels were treated with the active compound, the BDI score at Study Day 29 was significantly lower in the high-dose panel. It is notable that discontinuation of treatment at Study Day 30 resulted in a clear worsening of the HAM–D and BDI symptom scores until Study Day 32, before treatment with classical antidepressants was commenced.

In the high-dose panel, 8 of the 10 patients met the criterion of treatment response (a reduction in HAM–D score of at least 50% compared with screening), and 6 of these patients could be classified as remitters (a HAM–D score of 8 or less); in the low-dose panel, only 5 patients responded, with 3 of them achieving remission (see Zobel et al., 2000).

A similar picture emerged when anxiety symptoms were analyzed separately. The clinician ratings (Hamilton Rating Scale for Anxiety; Hamilton, 1996a) dropped significantly in both panels, whereas the patient ratings (State scale of the State–Trait Anxiety Inventory; Spielberger, Gorsuch, & Lushene, 1996) improved significantly only in the high-dose panel.

Four patients dropped out before completing the 30-day study, for different reasons. However, the findings were replicated in an intent-to-treat analysis applying the last observation carried forward approach (Zobel et al., 2000).

To further evaluate the antidepressant properties of NBI-30775/R121919, we compared the effect size measures obtained after 29 days of treatment with NBI-30775/R121919 with those obtained following 28 days of treatment with paroxetine (Nickel et al., 2003), which is a classical antidepressant acting as a selective serotonin reuptake inhibitor. Both studies were conducted with depressed inpatients from the same hospital, and comparable inclusion criteria and study procedures were used. As can be seen in Figure 2, the effect sizes of both drugs are highly comparable with regard to the HAM–D total score, the HAM–D Vegetative and Cognitive Depression subscales (Rhoades & Overall, 1983), and suicidality evaluated with respective items from the HAM–D, the Montgomery–Asberg Depression Rating Scale (Montgomery & Asberg, 1996), and the BDI. No significant differences were observed ($p > .235$), suggesting similar efficacy of NBI-30775/R121919 and paroxetine, despite the suboptimal dose regimen of NBI-30775/

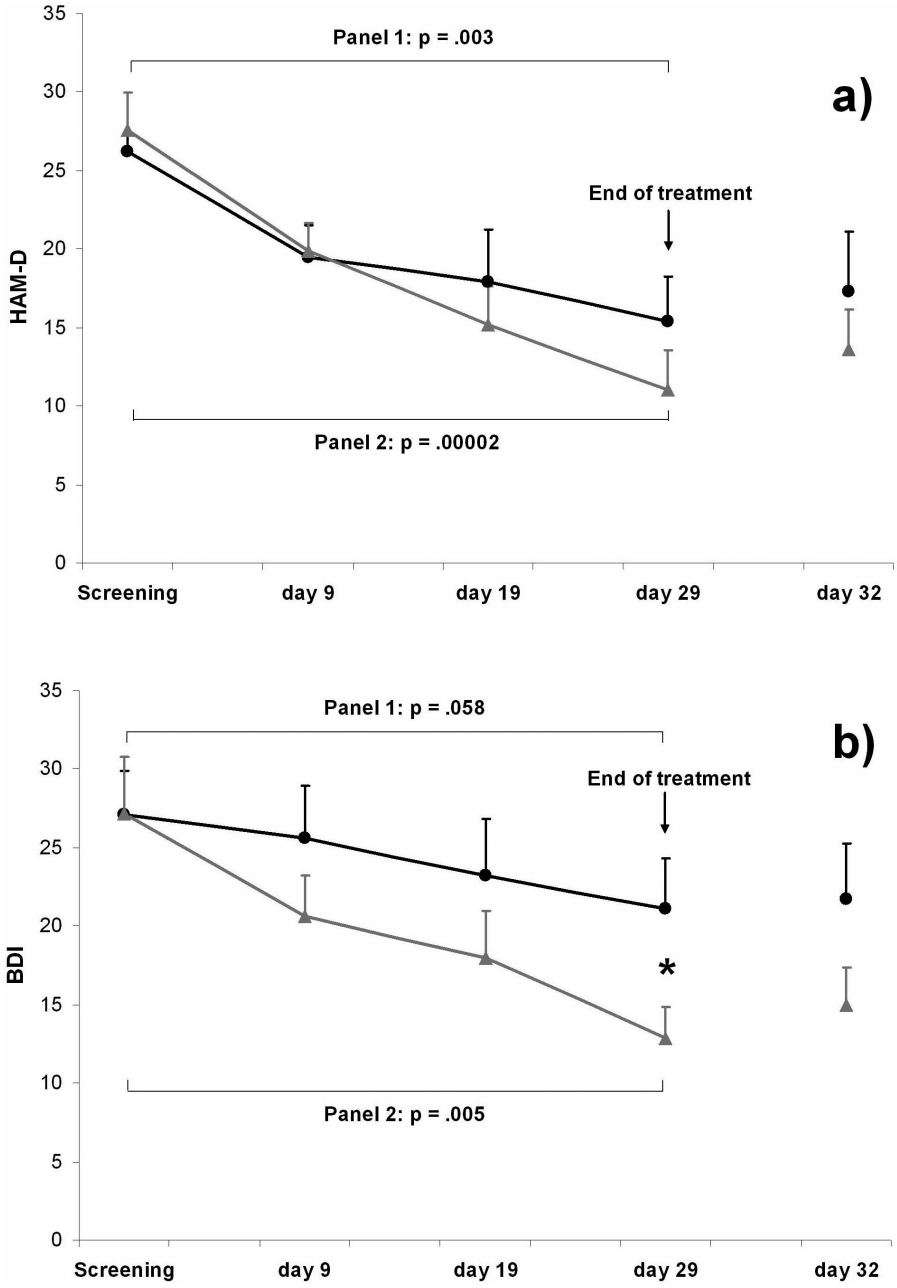

Figure 1. Change in Hamilton Rating Scale for Depression (HAM–D; a) and Beck Depression Inventory (BDI; b) rating scores in the low-dose (black lines) and high-dose (gray lines) NBI-30775/R121919 treatment groups (see also Zobel et al., 2000).

R121919, due to the fact that the CRH_1 antagonist study was primarily designed as a safety and tolerability study and not as a drug efficacy trial.

In addition to the psychopathological findings, sleep electroencephalogram (EEG) recordings were performed in a random subgroup of 10 patients before and after treatment with NBI-30075/R121919. The time spent in slow wave sleep, which is diminished in acute depression, increased in both panels; REM density, which is elevated in depressed patients, decreased in the high-dose panel but not in the low-dose panel, suggesting improved night sleep particularly in the high-dose panel.

Treatment with NBI-30775/R121919 was safe, with no serious side effects recorded during the trial. Circadian regulation of the HPA axis and its responsiveness to exogenous CRH stimulation was maintained (Zobel et al., 2000), and no impairment of other endocrine systems, including the hypothalamic–pituitary–gonadal axis, the hypotha-

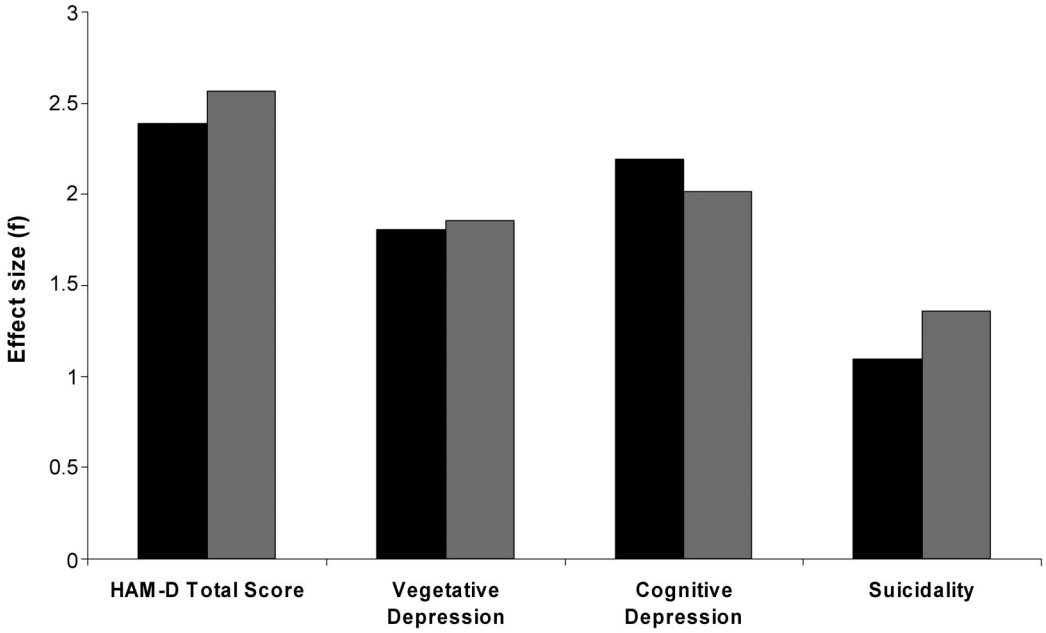

Figure 2. Effect size (*f*) of the Hamilton Rating Scale for Depression (HAM–D) total score, HAM–D Vegetative and Cognitive Depression subscales, and suicidality (evaluated with items from the HAM–D, Montgomery–Asberg Depression Rating Scale, and Beck Depression Inventory) after 4 weeks of treatment with 20–40 mg/day paroxetine (black bars) and 40–80 mg/day NBI-30775/R121919 (gray bars; see also Zobel et al., 2000; Nickel et al., 2003).

lamic–pituitary–thyroid axis, the renin–angiotensin system, and prolactin or vasopressin secretion, was observed. No negative effects on clinical laboratory parameters including liver enzymes, EEG, and electrocardiogram were recorded (Kunzel et al., 2003), and drug treatment did not alter plasma leptin levels or body weight of the patients (Kunzel et al., 2005).

Despite these very promising results, the development of NBI-30775/R121919 was halted because of an observation in an unpublished U.K. safety trial, where reversible increases of liver enzymes were observed in two subjects, apparently unrelated to the primary mode of action of this drug.

Randomized Placebo-Controlled Proof-of-Concept Study With NBI-34041

NBI-34041 is a nonpeptide tricyclic successor compound (Compound 12t) of NBI-30775/R121919 (Chen et al., 2004) with improved physiochemical properties for passing the blood–brain barrier, an effect that was achieved by reducing the overall lipophilicity of this compound (Gross et al., 2005). NBI-34041 binds with high affinity to cloned human CRH_1 receptors (Ki = 4.0 nmol/L), whereas binding to CRH_2 is not detectable with Ki greater than 10,000 nmol/L. Intragastric administration of NBI-34041 in rats inhibited the ACTH response to exogenously administered CRH in a dose-dependent manner, and oral gavage of NBI-34041 produced a significant attenuation of stress (footshock) induced ACTH release (Ising et al., in press).

Twenty-four healthy male volunteers participated in a randomized double-blind placebo-controlled dose-escalation and clinical proof-of-concept study (Ising et al., in press). Subjects received NBI-34041 in one of three dosages (10, 50, or 100 mg/day) or placebo over a time period of 14 days. To exclude the possibility that treatment with NBI-34041 might impair the responsiveness of the HPA axis, the authors conducted CRH stimulation tests at baseline and after 11 days of treatment. In these tests, plasma ACTH and cortisol responses to exogenous administration of 100 μg human CRH were evaluated. The results of the CRH stimulation test after 11 days of treatment with 100 mg/day NBI-34041 (the highest dose group) compared with the placebo group are presented in Figure 3. No significant differences were observed, suggesting that treatment with NBI-34041 over 11 days does not impair the responsiveness of the HPA axis to CRH in healthy male subjects. In addition to these findings, no systematic effects of NBI-34041 treatment on basal ACTH and cortisol plasma levels, urinary free cortisol concentrations, or circadian ACTH and cortisol secretion were observed, confirming that treatment with NBI-34041 was safe in all dose groups.

To evaluate its potential efficacy, the authors applied a psychosocial stress paradigm, the Trier Social Stress Test (TSST), to examine the ability of NBI-34041 to improve the stress response after subchronic treatment (9 days). The TSST is a standardized public-speaking procedure involving a mock job interview and mental arithmetic (Kirschbaum, Pirke, & Hellhammer, 1993; Zimmermann et al., 2004). After a 10-min preparation time, subjects gave a

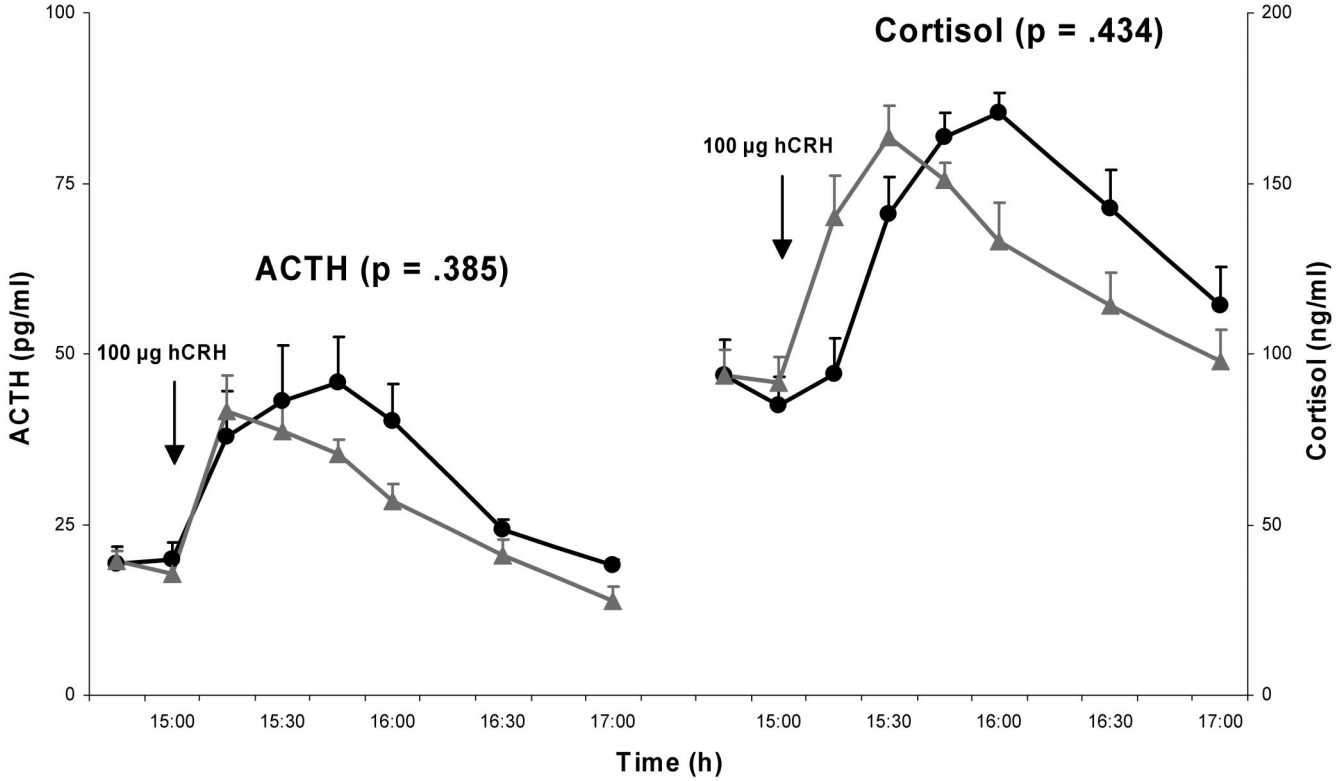

Figure 3. Response of adrenocorticotropic hormone (ACTH; left) and cortisol (right) to intravenous stimulation with 100 μg human corticotropin-releasing hormone (hCRH) after 11 days of treatment with 100 mg/day NBI-34041 (gray lines) or placebo (black lines; see also Ising et al., in press).

presentation to promote their candidacy for a position tailored to their education in front of an evaluating audience. After 5 min, subjects were given an unexpected mental arithmetic task for a further 5 min. Both tasks, mock job presentation and mental arithmetic, were videotaped to increase task engagement. All subjects presented with a similarly pronounced subjective stress response to this test (as measured by the State scale of the State–Trait Anxiety Inventory). HPA axis responses to the TSST, however, differed significantly between medication groups. The highest NBI-34041 dose group, who received 100 mg/day for 9 days, presented with a less pronounced cortisol response to the psychosocial stress procedure compared with the placebo group (see Figure 4).

These findings suggested that NBI-34041 did not alter the subjective response to the TSST, which corresponded on average with moderate tension, whereas the hormonal stress response was attenuated under NBI-34041. From a psychological point of view, moderate tension or vigor during a challenging task like the TSST is an important requirement for achieving optimal performance (Dickman, 2002) and, in combination with an attenuated stress hormone response, is the optimal prerequisite for mastering stressful challenges.

Further Compounds

Several drug companies are currently in the Phase I or Phase II stage of CRH_1 antagonist development. Neurocrine Biosciences, who have developed NBI-30775/R121919, NBI-34041, and several other compounds (Chen et al., 2004), continue with their CRH receptor program in partnership with GlaxoSmithKline. According to the Neurocrine Biosciences Web site, Phase I double-blind placebo-controlled trials are ongoing and GlaxoSmithKline planned to initiate Phase II trials in anxiety/depression in 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. Additionally, Taisho Pharmaceuticals reported on a CRH_1 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 I 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, are assumed to have CRH_1 receptor antagonists in their drug pipelines (Steckler

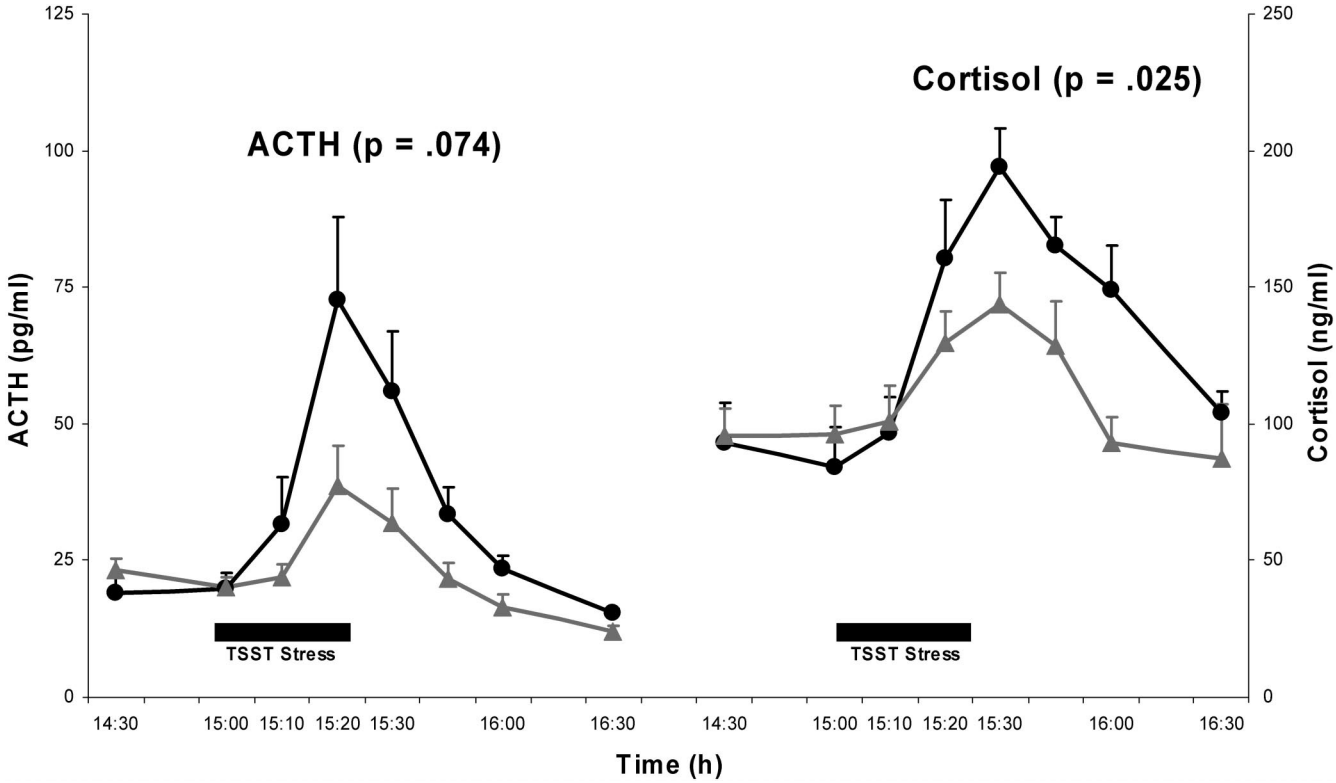

Figure 4. Response of adrenocorticotropic hormone (ACTH; left) and cortisol (right) to a standardized psychosocial stress test (the Trier Social Stress Test) after 9 days of treatment with 100 mg/day NBI-34041 (gray lines) or placebo (black lines; see also Ising et al., in press).

& Dautzenberg, 2006). However, no clinical data from any of these compounds have yet been made available for the public.

Conclusions and Future Directions

Clinical research has supported the hypothesis that CRH accounts not only for the neuroendocrine abnormalities seen in depression and anxiety but also for other signs and symptoms that are hallmarks of these clinical conditions. In fact, not only is CRH elevated in the cerebrospinal fluid of depressive patients (Nemeroff et al., 1984), but it decreases under antidepressant treatment (Heuser et al., 1998; Nemeroff et al., 1991). Likewise, a number of neuroendocrine function tests clearly indicate that normalization of abnormal HPA regulation, driven by CRH and other neuropeptides, is a prerequisite for successful antidepressant treatment (Appelhof et al., 2006; Aubry et al., 2007; Ising et al., 2007; Kunugi et al., 2006; Zobel et al., 2001; Zobel, Yassouridis, Frieboes, & Holsboer, 1999). These observations are in agreement with basic scientific studies in which suppression of CRH/CRH_1 signaling was observed to reduce anxiety-like behavior in animal models. These studies included administration of antisense directed against CRH_1 mRNA, selective CRH_1 antagonists, and transgenic mice carrying CRH_1 gene deletions (Muller & Holsboer, 2006). From these clinical and basic research efforts, the hypothesis was derived that the CRH_1 receptor might be a worthwhile drug target for novel antidepressants. Many pharmaceutical companies have initiated drug discovery and development programs aiming at novel CRH_1 antagonists; however, most of these programs have been put on hold because of untoward adverse effects of the chemical compounds used. These side effects were not related to CRH_1-directed pharmacology but rather were due to the pharmacophores used. This may explain why only a very limited number of clinical reports have appeared so far in the literature.

The studies summarized here support the view that CRH_1 antagonists have the potential as a new class of drugs for the treatment of stress-related diseases. The study investigating NBI-30775/R121919 in patients with depression not only showed antidepressive effects comparable to those of paroxetine but also demonstrated that the drug was specifically acting on the sleep-EEG profile in depressive patients in a way that was predicted from studies using rats. It is important to note that none of the patients studied showed any sign of hepatoxicity. In contrast, in the entire study population, liver enzymes were lower while patients were receiving NBI-30775/R121919 as compared with the antidepressant treatment that followed the trial medication.

The study investigating NBI-34041 used a different clinical endpoint, the stress hormone response to a psychosocial stressor. Here, the CRH_1 antagonist was capable of reducing the stress hormone secretion, again pointing to a drug-induced elevation of the stress response threshold. This finding has obvious implications for causality and—more specifically—for onset of depression, because stress exposure is an important trigger for the development of depression in predisposed individuals. According to the corticosteroid receptor hypothesis of depression, the signaling capacity of mineralo- and glucocorticoid receptors (MR and GR) is impaired in this disorder (Holsboer, 2000). As a consequence of an MR deficit, the threshold at the onset of the stress responses is lowered and signaling via CRH/CRH_1 pathways is facilitated. The peripheral stress hormone response is functionally dominated by enhanced plasma cortisol concentration, which exerts a negative feedback via GR. If GR function is impaired, the CRH/CRH_1 signaling remains insufficiently curtailed, resulting in a number of failed adaptations and finally in the development of disease. On the basis of these mechanisms and the herein reported study results with NBI-34041, it seems worthwhile to consider testing this and other CRH_1 antagonists as treatment to prevent development of stress-related disorders among those having experienced a severe trauma.

It is not yet clear what the ultimate role of CRH_1 antagonists in the treatment of depression and anxiety might be. The wealth of studies demonstrating that normalization of HPA regulation precedes beneficial antidepressant treatment response points to the possibility that clinical response to current antidepressants can be hastened by CRH_1 antagonist coadministration. 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 these compounds represent one of the most promising novel therapeutics in psychopharmacology.

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