

New directions in the development of antidepressants: the interface of neurobiology and psychiatry

Charles B. Nemeroff*

Emory University School of Medicine, Atlanta, Georgia, USA

There have been considerable advances in neurobiology in recent years that are providing new directions for the development of novel classes of antidepressants. For example, the finding that corticotropin-releasing factor (CRF) is hypersecreted in depressed patients and mediates certain symptoms of depression has led to the development of specific antagonists of the CRF₁ receptor. These are expected to prove highly effective for the treatment of mood and anxiety disorders. Another related avenue of research is based on evidence that cortisol is integral to the pathophysiology of major depression with psychotic features. One alternative for treating this subtype of affective disorder is, therefore, to block the action of glucocorticoids using a receptor antagonist such as mifepristone. These are just two of the many new directions that will likely lead to the development of antidepressants in the near future. Copyright © 2002 John Wiley & Sons, Ltd.

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INTRODUCTION

Remarkable advances in neuroscience have occurred in the past several years and these findings have provided considerable information relevant to the neurobiology of mood and anxiety disorders. Moreover, the recent completion of the human genome project will also undoubtedly have a significant impact in psychiatry. The sequencing of the 35 000 genes that comprise the human genome theoretically allow for the identification of vulnerability genes for mood disorders, both bipolar disorder and unipolar depression, and perhaps resistance. These genes, that confer either vulnerability or provide protection from severe psychiatric disorders, are likely to contribute pathophysiological information that will aid in the development of novel agents for the treatment of depression and other stress-

related psychiatric disorders. Advances in functional brain imaging will almost surely lead to the identification of specific deficits in neurotransmitters, or neurotransmitter transporters or neurotransmitter receptors, in individual patients and this is likely to improve our ability to predict treatment response to particular regimens for that patient. This review will consider just two of the new therapeutic approaches to the treatment of depression, a corticotropin-releasing factor (CRF)₁ receptor antagonist and glucocorticoid (GC) receptor antagonists.

CORTICOTROPIN-RELEASING FACTOR IN DEPRESSION AND ANXIETY

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that was first isolated and characterized in 1981 (Vale *et al.*, 1981). It is now well established that CRF orchestrates the central nervous system's control of the behavioural, endocrine, autonomic and immunological response to stress (Owens and Nemeroff, 1991; Heit *et al.*, 1997). CRF-containing cell bodies are distributed heterogeneously throughout the brain, with the highest density in the medial parvocellular division of the hypothalamic paraventricular

* Correspondence to: Dr C. B. Nemeroff, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1639 Pierce Drive, Atlanta GA 30322-4990, USA. Tel: +1 404 727 8382. Fax: +1 404 727 3233. E-mail: cnemor@emory.edu

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nucleus. This latter cell group forms part of the hypothalamic–pituitary complex that controls the secretion of adrenocorticotropin (ACTH) from the pituitary which, in turn, controls the secretion of the major stress hormone cortisol from the adrenal cortex. CRF is also found in a variety of other limbic and cortical brain areas including the central nucleus of the amygdala and the bed nucleus of the stria terminalis, and CRF neurones have extensive interactions with both the serotonergic and noradrenergic systems.

Two CRF receptor subtypes (CRF₁ and CRF₂) (Chalmers *et al.*, 1996) with distinct localization and receptor pharmacology have been cloned and sequenced. The CRF₁ receptor contains 415 amino acids and has a structure very similar to that of other G-protein coupled receptors. Antagonists at this receptor have been developed that show considerable promise as novel antidepressants and anxiolytics. The CRF₂ receptor is currently known to exist in two isoforms in rats and humans: the CRF_{2A} receptor that encodes a 411-amino acid G-coupled protein with about 70% homology to the CRF₁ receptor, and the CRF_{2B} receptor that contains an additional 20 amino acids in the N-terminal domain. The CRF₂ receptor appears to be linked to the control of eating behaviour and may show promise as a target for the treatment of bulimia and anorexia nervosa. The central nervous system distribution of the CRF₁ and CRF₂ receptor subtypes is also quite distinct. The CRF₁ receptor occurs with the greatest density in the cortex, the cerebellum and the pituitary, whereas the CRF₂ receptor is more abundant in the periphery and has a much more limited distribution in the brain where it is found mainly in the septum, ventromedial hypothalamus and dorsal raphe nucleus.

Central (intracerebroventricular) administration of CRF to laboratory animals results in a spectrum of behaviours strikingly similar to those of the depressive syndrome, including decreased appetite, sleep disruption, psychomotor alterations, decreased libido and reduction in exploratory behaviour (Owens and Nemeroff, 1991; Koob *et al.*, 1993; Dunn and Berridge, 1990). These findings, as well as the often-reported observation that depressed patients are hypercortisolaemic, led to the hypothesis that CRF may be hypersecreted in depressed patients. This is supported by numerous studies showing clearly elevated cerebrospinal fluid (CSF) concentrations of CRF in untreated depressed patients and suicide victims, but not in patients with other psychiatric disorders or in healthy volunteers (Arató *et al.*, 1986; Arató *et al.*, 1989; Bánki *et al.*, 1987; Bánki *et al.*, 1992a; France *et al.*, 1988; Nemeroff *et al.*, 1984). For

example, CSF CRF concentrations were markedly elevated in depressed patients compared with normal healthy controls and patients with schizophrenia, mania or Alzheimer's disease; levels were also elevated in patients with co-morbid Alzheimer's disease and depression (Bánki *et al.*, 1987). Similarly, in a study of patients with multi-infarct dementia, either alone or co-morbid with delirium or depression, CSF CRF levels were elevated only in the patients with co-morbid depression (Bánki *et al.*, 1992a). Patients with multiple sclerosis or Huntington's chorea with co-morbid depression also exhibit elevated CSF CRF concentrations (Kurlan *et al.*, 1988). Significant elevations in cisternal CSF CRF concentrations have also been reported in suicide victims compared with sudden death medical controls (Arató *et al.*, 1989). The critical common denominator is that all the studies reporting elevated CRF involved subjects suffering from moderate to severe depression. Only a small number of studies have been unable to replicate these findings, most likely due to the inclusion of subjects with mild or atypical depression.

This elevation in CRF secretion appears to be state-dependent as it can be normalized by successful treatment with a variety of antidepressants (fluoxetine, paroxetine, venlafaxine, desipramine and amitriptyline) and electroconvulsive therapy (ECT) (Bánki *et al.*, 1992b; Veith *et al.*, 1993; Nemeroff *et al.*, 1991). A number of selective CRF₁ receptor antagonists are also now in development and evidence indicates that they will prove to be highly effective in the treatment of depression and anxiety disorders.

PSYCHOTIC DEPRESSION

Major depression with psychotic features, or psychotic depression as it is commonly known, is a relatively common disorder that unfortunately often goes unrecognized. Up to 15% of patients with major depression have psychotic features and, in view of the fact that the annual incidence of major depression in the USA is approximately 25 million, if 15% of these patients are suffering from psychotic major depression, this represents an annual incidence of 3.75 million. This subtype of depression tends to run in families and is diagnostically probably the most homogeneous of all the subtypes of major depression. It also has a remarkably high recurrence rate and each episode is invariably similar.

Of all the subtypes of depression, psychotic depression undoubtedly has the lowest placebo response rate. It also responds poorly to antidepressant monotherapy, although there have been reports that the

selective serotonin reuptake inhibitor (SSRI) fluvoxamine is effective when given alone (Zanardi *et al.*, 1997; Gatti *et al.*, 1996). Although excellent results are usually achieved with ECT, the drawbacks of ECT treatment lead the vast majority of patients (about 80%) to be treated with a combination of an antipsychotic and an antidepressant (e.g. olanzapine or risperidone plus an SSRI). Although effective, such combination therapy may be associated with problems in terms of relapse and side-effect burden.

The role of glucocorticoid receptor antagonists in the treatment of psychotic depression

Patients with psychotic major depression have a considerably higher rate of dexamethasone non-suppression (i.e. cortisol hypersecretion due to hyperactivity of the pituitary–adrenal axis) than patients with non-psychotic major depression or healthy controls (Evans *et al.*, 1983; Nelson and Davis, 1997).

There is considerable evidence that cortisol is actually integral to the biology and pathophysiology of psychotic major depression. It has been suggested that high cortisol concentrations result in hyperactivity of dopamine neurons, as seen in schizophrenia, and it is this that results in the psychosis associated with psychotic depression (Schatzberg *et al.*, 1985). One novel treatment option for psychotic depression would therefore be to reduce the high cortisol levels using agents that block the synthesis of cortisol, such as metyrapone, aminoglutethamide and the antifungal agent ketoconazole. However, all of these drugs are problematic to use because of side-effects and potential untoward drug–drug interactions.

Corticosteroids enter the brain and bind to two forms of intracellular steroid receptors: the type 1 receptor that has a high affinity ($K_d = 0.5$ nm) and is known as the mineralocorticoid (MR) receptor and the type 2 receptor that has a low affinity ($K_d = 5$ nm) and is known as the glucocorticoid (GC) receptor. The structure of cortisol is similar to that of the steroid progesterone and the potent progesterone antagonist, mifepristone (RU 486), which is used for gynaecological and obstetric indications. Mifepristone, at high doses, also acts as an antagonist at GC but not MR receptors and there is evidence that it has efficacy in the management of psychotic depression. An anecdotal report published by van der Ley and colleagues suggested that mifepristone can reverse the psychosis resulting from excessive cortisol production in patients with Cushing's syndrome (van der Ley *et al.*, 1991). Based on these and other findings,

Bellano and colleagues (Bellano *et al.*, 2001) conducted a double-blind, placebo-controlled, crossover study to assess the effects of mifepristone in psychotic depression. The patients received a 600 mg dose of mifepristone followed by 4 days of placebo and then another 600 mg dose of mifepristone, with no wash-out period. The original pilot study enrolled five patients (3 male, 2 female). The Hamilton Depression Rating Scale (HAMD) total score fell significantly (31%) during mifepristone treatment compared with only a very small decline (7%) with placebo. The results were particularly striking in terms of the consistency and rapidity of the response. Similar results were obtained using the Brief Psychiatric Rating Scale (BPRS), with scores falling by 32.5% with mifepristone and only 0.5% with placebo, thus highlighting the efficacy of mifepristone on psychotic symptoms. A second study has now been conducted to assess different doses of mifepristone (50, 600 and 1200 mg). Changes in the BPRS score showed evidence of a dose-response with regard to reduction in psychosis, with a 32%, 40% and 52% reduction in the score with doses of 50, 600 and 1200 mg, respectively. Similarly, of eight patients enrolled in each group, there were only two responders (defined as $\geq 50\%$ decline in symptom severity) in the 50 mg group compared with seven in the 600 mg group and six in the 1200 mg group. A large-scale, placebo-controlled, double-blind trial is currently underway.

CONCLUSION

In the next five years we can expect to have available within our pharmacological armamentarium both a CRF_1 receptor antagonist for the treatment of depression and anxiety and a GC receptor antagonist for the rapid reversal of psychotic major depression. These are just two of the many examples of how further advances in neurobiology impact upon psychiatry. Indeed, it seems remarkable that the tricyclic antidepressants were developed only 40–50 years ago and there is now a wide array of drugs with different mechanisms of action available for the treatment of depression. In the future, it is certain that there will be a further increase in the number of antidepressants available to treat this devastating disorder.

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