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

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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 CRF_1 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.

KEY WORDS — antidepressants; depression; psychotic depression; CRF receptors; glucocorticoid receptors

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 heterogenously throughout the brain, with the highest density in the medial parvocellular division of the hypothalamic paraventricular

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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 (CRF_1 and CRF_2) (Chalmers *et al.*, 1996) with distinct localization and receptor pharmacology have been cloned and sequenced. The CRF_1 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 CRF_2 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 CRF_1 receptor, and the CRF_{2B} receptor that contains an additional 20 amino acids in the *N*-terminal domain. The CRF_2 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 CRF_1 and CRF_2 receptor subtypes is also quite distinct. The CRF_1 receptor occurs with the greatest density in the cortex, the cerebellum and the pituitary, whereas the CRF_2 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 CRF_1 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 (ven der Ley *et al.*, 1991). Based on these and other findings, Bellanof and colleagues (Belanoff *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 washout 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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REFERENCES

Arató M, Bánki CM, Bissette G, Nemeroff CB. 1989. Elevated CSF CRF in suicide victims. *Biol Psychiat* **24**: 355–359.

Arató M, Bánki CM, Nemeroff CB, Bissette G. 1986. Hypothalamic–pituitary axis and suicide. *Ann New York Acad Sci* **487**: 263–270.

Bánki CM, Bissette G, Arató M, O'Connor L, Nemeroff CB. 1987. Cerebrospinal fluid corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. *Am J Psychiat* **144**: 873–877.

Bánki CM, Karmacsi L, Bissette G, Nemeroff CB. 1992a. Cerebrospinal fluid neuropeptides in mood disorders and dementia. *J Affect Disord* **25**: 39–46.

Bánki CM, Karmacsi L, Bissette G, Nemeroff CB. 1992b. CSF corticotropin-releasing hormone and somatostatin in major depression: response to antidepressant treatment and relapse. *Eur Neuropsychopharmacol* **2**: 107–113.

Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF. 2001. Rapid reversal of psychotic depression using mifepristone. *J Clin Psychopharmacol* **21**: 516–521.

Chalmers DT, Lovenberg TW, Grigoriadis DE, Behan DP, Desouza EB. 1996. Corticotropin-releasing factor receptors: from molecular biology to drug design. *Trends Pharmacol Sci* **17**: 166–172.

Dunn AJ, Berridge CW. 1990. Physiological and behavioral responses to corticotropin-releasing factor administration: is CRF a mediator of anxiety or stress response? *Brain Res Rev* **15**: 71–100.

Evans DL, Burnett GB, Nemeroff CB. 1983. The dexamethasone suppression test in the clinical setting. *Am J Psychiatry* **140**: 586–589.

France RD, Urban B, Krishnan KRR, *et al.* 1988. CSF corticotropin-releasing factor-like immunoreactivity in chronic pain patients with and without major depression. *Biol Psychiat* **23**: 86–88.

Gatti F, Bellini L, Gasperini M, Perez J, Zanardi R, Smeraldi E. 1996. Fluvoxamine alone in the treatment of delusional depression. *Am J Psychiatry* **153**: 414–416.

Heit S, Owens MJ, Plotsky PM, Nemeroff CB. 1997. Corticotropin-releasing factor, stress and depression. *The Neuroscientist* **3**: 186–194.

Koob GF, Heinrichs SC, Pich EM. 1993. The role of corticotropin-releasing factor in behavioral response to stress. In *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, De Souza EB, Nemeroff CB (eds). John Wiley and Sons: Chichester; 277–295.

Kurlan R, Caine E, Rubin A, *et al.* 1988. Cerebrospinal correlates of depression in Huntington's disease. *Arch Neurol* **45**: 881–883.

Nelson JC, Davis JM. 1997. DST studies in psychotic depression: a meta-analysis. *Am J Psychiatry* **154**: 1497–1503.

Nemeroff CB, Bissette G, Akil H, Fink M. 1991. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *Br J Psychiatry* **158**: 59–63.

Nemeroff CB, Widerlöv E, Bissette G, *et al.* 1984. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* **226**: 1342–1344.

Owens MJ, Nemeroff CB. 1991. Physiology and pharmacology of corticotropin-releasing factor. *Pharmacol Rev* **43**: 425–473.

Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO. 1985. A corticosteroid/dopamine hypothesis for psychotic depression and related states. *J Psychiatr Res* **19**: 57–64.

Vale W, Speiss J, Rivier C, Rivier J. 1981. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* **213**: 1394–1397.

van der Ley AJ, Foeken K, van der Mast RC, Lamberts SW. 1991. Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med* **114**: 143–144.

Veith RC, Lewis N, Langohr JI, *et al.* 1993. Effect of desipramine on cerebrospinal fluid concentrations of corticotropin-releasing factor in human subjects. *Psychiatry Res* **46**: 1–8.

Zanardi R, Franchini L, Gasperini M, Smeraldi E, Perez J. 1997. Long-term treatment of psychotic (delusional) depression with fluvoxamine: an open pilot study. *Int Clin Psychopharmacol* **12**: 195–197.

