· 综述与述评 ·

Glucocorticoid receptor and treatment of psychotic major depression

HUI Xin, ZHOU Cai-hong, WANG Ming-wei*

(*The National Center for Drug Screening, Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences; Graduate School of the Chinese Academy of Sciences, Shanghai 201203, China*)

Key words: psychotic major depression; hypercortisolemia; hypothalamic-pituitary-adrenal axis; glucocorticoid receptor; antagonist

CLC number: R749.42; R971.43 **Document code:** A **Article ID:** 0513 - 4870(2005)11 - 0961 - 06

糖皮质激素受体与重型精神病性抑郁症的治疗

惠 昕, 周彩红, 王明伟*

(中国科学院 上海生命科学研究院 药物研究所 国家新药筛选中心; 中国科学院 研究生院, 上海 201203)

关键词: 重型精神病性抑郁症; 肾上腺皮质醇增多症; 下丘脑 垂体 肾上腺轴; 糖皮质激素受体; 拮抗剂

1 Introduction

Psychotic major depression (PMD), which responds poorly to tricyclic anti-depressants, is a distinct syndrome of depression. Hypercortisolemia (cortisone hypersecretion), a biological abnormality existing in many patients with PMD, has led to various theoretical and empirical rationales for the potential therapeutic use of anti-glucocorticoid agents in the treatment of depression. Most available anti-depressant medications today increase brain levels of glucocorticoid receptor (GR), rendering individuals more sensitive to corticosteroid negative feedback regulated by hypothalamic-pituitary-adrenal (HPA) axis. Recently, several studies have assessed the behavioral effects of direct pharmacological lowering of cortisol levels in patients with PMD using GR antagonists, such as RU486 (mifepristone). Randomized and controlled studies have shown that GR antagonists are capable of significantly improving psychosis and depression symptoms of PMD patients, and thus pointing to a promising potential of developing GR antagonist as a novel anti-depressant agent to revolutionize the treatment of depression.

2 Pathophysiology of PMD

PMD is a mental disorder with considerable morbidity and mortality. Numerous studies, relative to its clinical characteristics, biological measures, treatment course and outcome, and familial history, suggest that PMD is a distinct subtype of depression[1]. Twenty-five percent of the patients hospitalized for major depression met the diagnostic criteria for PMD[2], and 14.7% of the outpatients had a history of psychotic characteristics[3,4]. Patients with PMD exhibit pronounced paranoid symptoms, cognitive impairment, hopelessness, hypochondriasis, anxiety, insomnia, absence of diurnal variation, and constipation[2,5]. Symptom relapse or recurrence is a common feature and suicidal risks are much higher than non-psychotic depression patients[6]. The prevalence is higher (45%) in elderly patients with major depression, but PMD can occur in all ages. PMD is hard to diagnose, because psychosis may be subtle, intermittent, or concealed, and anti-depressant therapy alone often results in poor efficacy[3,4,7].

Received date: 2005-01-28.

Foundation item: The Ministry of Science and Technology of China (2002AA2Z343A); Chinese Academy of Sciences (KSCX1-SW-11-2); Shanghai Municipality Science and Technology Development Fund (03dz19224).

* Corresponding author Tel: 86 - 21 - 50800598,
Fax: 86 - 21 - 50800721,
E-mail: mwwang@siniwest.com

Although PMD patients do respond to combinations of currently available anti-psychotic and anti-depressant medications, and electroconvulsive therapy (ECT), these therapies act very slowly, which lead to an interim period of high morbidity. ECT remains the therapy of choice today.

An association of HPA axis activity and mental disturbances was first reported about 50 years ago[8]. It was found that depressed patients with suicidal behavior in their past and recent disease history showed a differentially regulated HPA system compared with depressed patients without suicidal behavior[9]. In the case of PMD, a series of studies revealed that: (1) a majority of PMD patients tested abnormally for dexamethasone suppression while patients with non-affective psychoses (eg, schizophrenia) did not show this feature; (2) both peripheral cortisol and adrenocorticotropin hormone (ACTH) levels were elevated in patients with PMD; (3) ECT could cause a perturbation of the HPA axis[10]. Latest experimental data demonstrated that selective removal of forebrain GR uncovered a substantial loss in negative feedback, causing sustained increases in circulating stress hormones. This increase could then elicit sequelae that resemble the effects of depression[11]. These findings support the neuroendocrine hypothesis that dysregulation in the HPA axis plays an important role in the pathogenesis and development of PMD, and can explain why PMD is often associated with cognitive impairment[2].

Hypercortisolemia may activate serotonergic, dopaminergic and noradrenergic neurons in the brain stem thereby increasing the sensitivity of limbic-forebrain areas to aminergic inputs[12]. Dopaminergic system activation and higher levels of cerebrospinal fluid 5-hydroxyindoleacetic acid were reported in PMD patients[3]. In addition, PMD patients have lower serum dopamine-β-hydroxylase (DBH) activity (the enzyme that converts dopamine to norepinephrine)[13] leading to an enhancement of dopamine activity and psychotic behavior[14].

Besides neuroendocrine changes in PMD patients, larger ventricle-to-brain ratios and greater atrophy in parietal regions were demonstrated by Rothschild and colleagues[15]. Diencephalic atrophy, reticular activating system lesions, brain stem atrophy, and left-sided frontotemporal atrophy were also noted[16]. These structural alterations were correlated with impairment in motor function, attention, memory, and visual-spatial skills.

3 Involvement of GR

Following stimulation, the HPA axis secretes cortisol from the adrenal glands, which in turn inhibits both corticotrophin-releasing hormone (CRH) and ACTH release from the hypothalamus or pituitary gland. This feedback mechanism involves two types of adrenal steroid receptors, namely, mineralocorticoid receptor (MR, type I) and glucocorticoid receptor (GR, type II). MR mediates the circadian through basal level of corticosteroids, whereas GR ensures a high level of glucocorticoid during circadian peak and stress[17]. GR is a hormone-activated transcription factor consisting of two subtypes, GRα and GRβ. They have different carboxy termini and only GRα binds to cortisol[18]. "Inactivated" GR resides primarily in the cytoplasm associated with a multimeric complex of chaperone proteins including heat shock proteins (HSPs). Upon steroid binding, GR undergoes a conformational change ("activation"), dissociates itself from the chaperone complex, and translocates to the nucleus, where it either binds to glucocorticoid response elements (GREs) on DNA or interacts with other transcriptional factors[19]. GR is most abundant in hypothalamic CRH neurons and pituitary corticotropes[12]. In the human brain, the abundance of GRβ is far less than that of GRα[18], and GRs are very responsive to changes of cortisol concentrations[12]. Survivors of GR knockout rats displayed hypertrophy and hyperplasia of the adrenal glands, with corticosterone production enhanced 3-fold, and ACTH levels increased 10-fold[20]. GR appears to "switch off" cortisol production upon stress and thus maintains homeostasis, the balance between stimulative and inhibitory influences.

A set of studies have suggested that high levels of GR in the brain can make the animal behave in a more anxious or depressive manner and that, conversely, blocking the receptors with an antagonist or knocking it down in brain can make the animal appear less anxious. For example, GR-disrupted mice not only exhibited aberrant memories, but also adopted a differential search strategy, as tested in a Morris water maze[21]. In GR-dim/dim mutants, a selective impairment of spatial memory was observed[22]. Transgenic mice expressing anti-sense RNA against GR had a diminished, but not absent, GR function, accompanied by a reduction in CRH neurons of the hypothalamus with no effect on corticosterone

levels[23]. In contrast, complete inactivation of the GR gene in the mouse central nervous system led to increases in hypothalamic CRH production and plasma corticosterone concentrations[24]. It is noteworthy that both strains of mice displayed a phenotype characterized by reduced anxiety, suggesting a role of GR in regulating emotional behavior[25]. Further studies indicate that GR is not only a regulator of stress responsiveness but also a key controller of emotional lability[26].

The above observations were confirmed recently in a line of mice with time-dependent, forebrain-specific disruption of GR (FBGRKO)[27] using the Cre-loxP system[28]. These mice developed a number of both physiological and behavioral abnormalities that mimicked major depressive disorder in humans, including hyperactivity of the HPA axis, impaired negative feedback regulation of the HPA axis, and increased depression-like behavior. Importantly, a number of these abnormalities are normalized by chronic treatment with the tricyclic anti-depressant, imipramine[27].

As far as receptor pathology is concerned, cumulative evidence suggests that neither cytosolic GR levels nor its binding affinity to glucocorticoid were altered in patients with PMD[29]. A decreased GR mRNA level was detected in the frontal cortex and hippocampus of certain psychiatric subjects by one group[29], but the result could not be verified by others[30]. Individuals with familial glucocorticoid resistance had impaired HPA feedback and deficient GR function leading to hypercorticoidism[12], for which an altered GRα/GRβ ratio may be responsible[31]. Furthermore, results of several human GR polymorphism studies could not establish a clear linkage between amino acid substitutions or nucleotide changes in a number of psychiatric disorders[20]. These investigations imply that excessive HPA axis activity found in PMD patients is most likely a phenotypic or functional deviation on the part of GR.

4 Treatment with GR antagonists

A couple of anti-glucocorticoid strategies have been employed in PMD therapy: (1) cortisol synthesis inhibitors, such as metyrapone, aminoglutethimide and ketoconazole; and (2) dehydroepiandrosterone (DHEA) —— a steroid compound with anti-glucocorticoid properties[32]. In addition, a CRH receptor antagonist —— R121919, that reduces the release of ACTH and hence, the peripheral corticosterone level, was shown to improve affective symptoms in patients with major depression[33]. However, the efficacy of these treatments in hypercortisolemia psychotic and non-psychotic depressed patients were less than ideal[3]. A major concern of using these medications relates to significant side-effects, including the potential for adrenal insufficiency and hepatic damage.

Another approach is the use of GR antagonists, such as RU486 (mifepristone), that does not inhibit steroid biosynthesis but block GR actions at higher doses. RU486 is a potent anti-progesterone and anti-glucocorticoid agent in humans, and its pharmacological effects are realized via suppression of the interaction between native ligands and their respective receptors. The mechanism, by which RU486 exerts its antagonistic action, has been shown to be an active process (recruitment of co-repressors during transcription)[34], in addition to receptor blockade, as revealed by the three-dimensional crystal structures of hGR[35]. Following RU486 administration, endocrine function is perturbed initially but a new balance within the HPA axis would soon be established to adequately manage circulating levels of RU486 and endogenous cortisol[36].

RU486 was successfully applied to the treatment of Cushing's disease[37]. The efficacy was validated in another group of patients who simultaneously developed psychosis/depression and Cushing's syndrome[37,38]. A preliminary study involving 8 patients with chronic, non-psychotic depression was conducted in 1993. RU486 (200 mg• d^{-1}), given orally for 8 weeks, only achieved modest improvement in 3 of the 4 subjects[39]. This was followed by a small, double-blind, placebo-controlled, crossover study (600 mg• d^{-1} × 4) in 5 patients with PMD[40]. All patients showed substantial improvement in their HAM-D (Hamilton Rating Scale for Depression) scores while receiving RU486, and 4 of the 5 patients displayed marked improvement in their BPRS (Brief Psychotic Rating Scale) scores. Thereafter, Belanoff and his colleagues carried out an open-label trial in 30 PMD patients with HAM-D scores of 18 or greater. The subjects were randomly assigned to receive 50, 600, or 1 200 mg of RU486 once daily for 7 days, and all of them completed the protocol. While side-effects were mild and sporadic, patients in the two high dose groups showed significant reduction in their symptoms within 7 days or less: 40% had a greater than 50% decrease in

their HAM-D scores and over 60% demonstrated at least a 30% reduction in BPRS scores. This approach produced more rapid effects than atypical anti-psychotic/anti-depressant combination therapy, and was well accepted compared to ECT. These encouraging efficacy data led to two separate, randomized, double-blind, placebo-controlled clinical trials (600 mg of RU486 daily × 7 plus 28-day follow-up) enrolling approximately 400 in-patients. Patients in the first trial were stabilized on existing medication regimens prior to RU486 therapy while concomitant treatment was not allowed in the second trial. Interim data suggest that RU486 is markedly more likely than placebo to effect a rapid and sustained remission in PMD patients[41]. Meanwhile, another steroidal GR antagonist, ORG34517, was studied side-by-side with RU486. It was found that both compounds were superior to placebo or certain anti-depressants in treating PMD in terms of onset of action and clinical efficacies[42].

Latest investigations with 20 PMD subjects taking no psychotropic medications demonstrate that 6-day course of RU486 (for 8 weeks) significantly improved HAM-D and CGI (clinical global impressions) scores after 1 week and between weeks 1 and 4, and BPRS scores after 4 weeks. Although this study was not blinded and without placebo control, the outcome points to the clinical usefulness of relatively longer time RU486 intervention in the absence of concomitant anti-depressant administration[43].

Short-term suppression of GR by RU486 helps to reset a putative dysfunctional glucocorticoid negative feedback mechanism in depressed patients[7]. High levels of glucocorticoids activate GR and inhibit neuronal excitability as GR activation may favor long-term depression via potentiation suppression. It is possible that RU486 antagonizes these actions and, under conditions of high cortisol, can improve cognition in patients with PMD, schizophrenia, unipolar or bipolar disorder[44]. This might be the molecular basis by which GR antagonists exert their therapeutic effects on PMD.

Cymipristone (Figure 1) was synthesized based on the structure of RU486. It has a different metabolic profile as oppose to that of RU486 when used in humans, with a comparable GR antagonistic activity[45]. Although multi-center clinical trials for a reproductive indication are still ongoing, it is expected that this new chemical entity will soon be evaluated for PMD therapy.

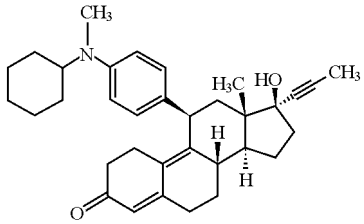

Figure 1 Structure of cymipristone

5 Perspective

There is a strong evidence to support the hypothesis that PMD is a distinct syndrome. Statistically significant differences exist between patients with PMD, specifically exhibiting abnormalities in the HPA axis activity and markedly elevated cortisol levels, and those with non-psychotic major depression. Regardless of various factors that lead to susceptibility to depression, it is likely that the disease process sooner or later engages the stress system. Stress in turn can contribute to the deteriorating course of the illness. Both overactivation and underactivation of the stress response are damaging to humans, and effective treatment of depression requires the "resetting" of the controlling mechanism(s). This can often be achieved through classical anti-depressants, but sometimes may need direct intervention by altering specific molecular components of the regulatory system to restore its balance[11].

PMD patients have a very low placebo response rate, as well as poor response to anti-depressant therapy alone. Hypercortisolemia, a clinical manifestation repeatedly demonstrated in many patients with PMD, has led to the use of anti-glucocorticoid agents for depression therapy. Some degree of efficacy has been seen with these drugs, but not without serious side-effects, such as hypoadrenalism and hepatotoxicity. The introduction of anti-depressants with novel mechanisms of action could potentially revolutionize the treatment of depression, and the rationale of treating PMD patients with GR antagonists is well-supported by both laboratory and clinical experiences. Type II GR antagonists are much more specific than ECT. One such agent, RU486, is being studied for the treatment of patients with PMD and has been reported to improve psychosis and depression symptoms in randomized, controlled studies. Since GR blockage or deprivation is also efficacious in major depression[33], schizophrenia[44] and bipolar disorder[46], the dysfunction of the HPA axis may

prove to be a common feature in mentally ill patients with diverse clinical manifestations. Interventional targets will include a variety of aspects along the regulatory pathway of the HPA axis. New therapeutic agents are currently being sought with the hope of finding a more selective, efficacious and safe drug that will improve the symptoms of psychosis that often leads to suicide in this patient population.

Acknowledgement: We are indebted to Dr. D. E. Mais for critical review of the manuscript.

References

[1] Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? [J]. *Am J Psychiatry*, 1992, **149**(6): 733 - 745.

[2] Fleming SK, Blasey C, Schatzberg AF. Neuropsychological correlates of psychotic features in major depressive disorders: a review and meta-analysis [J]. *J Psychiatr Res*, 2004, **38**(1): 27 - 35.

[3] Rothschild AJ. Challenges in the treatment of depression with psychotic features [J]. *Biol Psychiatry*, 2003, **53**(8): 680 - 690.

[4] Schatzberg AF. New approaches to managing psychotic depression [J]. *J Clin Psychiatry*, 2003, **64**(Suppl 1): 19 - 23.

[5] Nelson EB, Sax KW, Strakowski SM. Attentional performance in patients with psychotic and nonpsychotic major depression and schizophrenia [J]. *Am J Psychiatry*, 1998, **155**(1): 137 - 139.

[6] Vythilingam M, Chen J, Bremner JD, *et al*. Psychotic depression and mortality [J]. *Am J Psychiatry*, 2003, **160**(3): 574 - 576.

[7] Gold PW, Drevets WC, Charney DS. New insights into the role of cortisol and the glucocorticoid receptor in severe depression [J]. *Biol Psychiatry*, 2002, **52**(5): 381 - 385.

[8] Quarton GC, Clark LD, Cobb S, *et al*. Mental disturbances associated with ACTH and cortisone: a review of explanatory hypotheses [J]. *Medicine (Baltimore)*, 1955, **34**(1): 13 - 50.

[9] Pfennig A, Kunzel HE, Kern N, *et al*. Hypothalamus-pituitary-adrenal system regulation and suicidal behavior in depression [J]. *Biol Psychiatry*, 2005, **57**(4): 336 - 342.

[10] Posener JA, DeBattista C, Williams GH, *et al*. 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression [J]. *Arch Gen Psychiatry*, 2000, **57**(8): 755 - 760.

[11] Akil H. Stressed and depressed [J]. *Nat Med*, 2005, **11**(2): 116 - 118.

[12] de Kloet ER, Vreugdenhil E, Oitzl MS, *et al*. Brain corticosteroid receptor balance in health and disease [J]. *Endocrine Rev*, 1998, **19**(3): 269 - 301.

[13] Mod L, Rihmer Z, Magyar I, *et al*. Serum DBH activity in psychotic vs. nonpsychotic unipolar and bipolar depression [J]. *Psychiatry Res*, 1986, **19**(4): 331 - 333.

[14] Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis [J]. *Am J Psychiatry*, 1997, **154**(11): 1497 - 1503.

[15] Rothschild AJ, Benes F, Hebben N, *et al*. Relationships between brain CT scan findings and cortisol in psychotic and nonpsychotic depressed patients [J]. *Biol Psychiatry*, 1989, **26**(6): 26565 - 26575.

[16] Simpson S, Baldwin RC, Jackson A, *et al*. The differentiation of DSM-III-R psychotic depression in later life from nonpsychotic depression: comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features [J]. *Biol Psychiatry*, 1999, **45**(2): 193 - 204.

[17] Bachmann CG, Linthorst AC, Holsboer F, *et al*. Effect of chronic administration of selective glucocorticoid receptor antagonists on the rat hypothalamic-pituitary-adrenocortical axis [J]. *Neuropsychopharmacology*, 2003, **28**(6): 1056 - 1067.

[18] Oakley RH, Sar M, Cidlowski JA. The human glucocorticoid receptor beta isoform [J]. *J Biol Chem*, 1996, **271**(16): 9550 - 9559.

[19] Pratt WB. The role of heat shock proteins in regulating the function, folding, and trafficking of the glucocorticoid receptor [J]. *J Biol Chem*, 1993, **268**(29): 21455 - 21458.

[20] DeRijk RH, Schaaf M, de Kloet ER. Glucocorticoid receptor variants: clinical implications [J]. *J Steroid Biochem Mol Biol*, 2002, **81**(2): 103 - 122.

[21] Oitzl MS, de Kloet ER, Joels M, *et al*. Spatial learning deficits in mice with a targeted glucocorticoid receptor gene disruption [J]. *Eur J Neurosci*, 1997, **9**(11): 2284 - 2296.

[22] Oitzl MS, Reichardt HM, Joels M, *et al*. Point mutation in the mouse glucocorticoid receptor preventing DNA binding impairs spatial memory [J]. *Proc Natl Acad Sci USA*, 2001, **98**(22): 12790 - 12795.

[23] Dijkstra I, Tilders FJ, Aguilera G, *et al*. Reduced activity of hypothalamic corticotropin-releasing hormone neurons in transgenic mice with impaired glucocorticoid receptor function [J]. *J Neurosci*, 1998, **18**(10): 3909 - 3918.

[24] Tronche F, Kellendonk C, Kretz O, *et al*. Disruption of the glucocorticoid receptor gene in the nervous system results in reduced anxiety [J]. *Nat Genet*, 1999, **23**(1): 99 - 103.

[25] Gass P, Reichardt HM, Strekalova T, *et al*. Mice with targeted mutations of glucocorticoid and mineralocorticoid receptors: models for depression and anxiety? [J]. *Physiol Behav*, 2001, **73**(5): 811 - 825.

[26] Wei Q, Lu XY, Liu L, *et al*. Glucocorticoid receptor

overexpression in forebrain: a mouse model of increased emotional lability [J]. *Proc Natl Acad Sci USA*, 2004, **101**(32): 11851 - 11856.

[27] Boyle MP, Brewer JA, Funatsu M, *et al*. Acquired deficit of forebrain glucocorticoid receptor produces depression-like changes in adrenal axis regulation and behavior [J]. *Proc Natl Acad Sci USA*, 2005, **102**(2): 473 - 478.

[28] Wintermantel TM, Berger S, Greiner EF, *et al*. Evaluation of steroid receptor function by gene targeting in mice [J]. *J Steroid Biochem Mol Biol*, 2005, **93**: 107 - 112.

[29] Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment [J]. *Biol Psychiatry*, 2001, **49**(5): 391 - 404.

[30] Lopez JF, Chalmers DT, Little KI, *et al*. Regulation of serotonin 1A, glucocorticoid and mineralocorticoid receptor in rat and human hippocampus [J]. *Biol Psychiatry*, 1998, **43**(8): 547 - 573.

[31] Juruena MF, Cleare AJ, Bauer ME, *et al*. Molecular mechanisms of glucocorticoid receptor sensitivity and relevance to affective disorders [J]. *Acta Neuropsychiatrica*, 2003, **15**(6): 354 - 367.

[32] Reus VI, Wolkowitz OM, Frederick S. Antiglucocorticoid treatments in psychiatry [J]. *Psychoneuroendocrinology*, 1997, **22**(Suppl): Sl21 - Sl24.

[33] Zobel AW, Nickel T, Künzel HE, *et al*. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated [J]. *J Psychiatr Res*, 2000, **34**(3): 171 - 181.

[34] Schulz M, Eggert M, Baniahmad A, *et al*. RU486-induced glucocorticoid receptor agonism is controlled by the receptor N terminus and by corepressor binding [J]. *J Biol Chem*, 2002, **277**(29): 26238 - 26243.

[35] Kauppi B, Jakob C, Farnegardh M, *et al*. The three-dimensional structures of antagonistic and agonistic forms of the glucocorticoid receptor ligand-binding domain: RU-486 induces a transconformation that leads to active antagonism [J]. *J Biol Chem*, 2003, **278**(25): 22748 - 22754.

[36] Bertagna X, Escourolle H, Pinquier JL, *et al*. Administration of RU 486 for 8 days in normal volunteers: antiglucocorticoid effect with no evidence of peripheral cortisol deprivation [J]. *J Clin Endocrinol Metab*, 1994, **78**(2): 375 - 380.

[37] van der Lely AJ, Foeken K, van der Mast RC, *et al*. Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486) [J]. *Ann Intern Med*, 1991, **114**(2): 143 - 144.

[38] Chu JW, Matthias DF, Belanoff J, *et al*. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486) [J]. *J Clin Endocrinol Metab*, 2001, **86**(8): 3568 - 3573.

[39] Murphy BE, Filipini D, Ghadirian AM. Possible use of glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU 486 [J]. *J Psychiatry Neurosci*, 1993, **18**(5): 209 - 213.

[40] Belanoff JK, Flores BH, Kalezhan M, *et al*. Rapid reversal of psychotic depression using mifepristone [J]. *J Clin Psychopharmacol*, 2001, **21**(5): 516 - 521.

[41] Belanoff JK, DeBattista C. Mifepristone in psychotic major depression [J]. *Biol Psychiatry*, 2004, **55**: 1S - 242S.

[42] Pinder RM. Glucocorticoid antagonists in depression [J]. *Biol Psychiatry*, 2004, **55**: 1S - 242S.

[43] Simpson GM, El Sheshai A, Loza N, *et al*. An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression [J]. *J Clin Psychiatry*, 2005, **66**(5): 598 - 602.

[44] Gallagher P, Watson S, Smith MS, *et al*. Effects of adjunctive mifepristone (RU-486) administration on neurocognitive function and symptoms in schizophrenia [J]. *Biol Psychiatry*, 2005, **57**(2): 155 - 161.

[45] Chen LZ, Zuo L, Wang MW, *et al*. Steroids, their preparation, pharmaceutical compositions thereof and uses of the compounds [P]. *US Pat*: 6514956B1, 2003-02-04.

[46] Young AH, Gallagher P, Watson S, *et al*. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder [J]. *Neuropsychopharmacology*, 2004, **29**: 1538 - 1545.