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Current antidepressant drugs

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INTRODUCTION

The history of effective antidepressants began with the accidental discovery of monoamine oxidase inhibitors (MAOI's) and tricyclic antidepressants (TCA's) in the 1950's. Once their therapeutic efficacy had been established, detailed studies of their pharmacological and biochemical properties indicated that their activity was associated with an enhancement of monoaminergic function. This formed the basis of the monoamine hypothesis of depression which postulated that the core symptoms of depression are associated with a functional defect in noradrenaline and serotonin[1,2]. Most conventional antidepressants are thought to act by enhancing noradrenergic and/or serotonegic function either by inhibiting the metabolism of the monoamine transmitters (MAOI's), by inhibiting the monoamine transporter and thereby prolonging the action of the transmitter at the postsynaptic receptor sites (TCA's and most second generation antidepressants such as the selective serotonin reuptake inhibitors (SSRI's), or by enhancing the release of one of the monoamines (the tetracyclic compounds mirtazepine and mianserin enhance the release of noradrenaline for example). By the early 1970's the monoamine hypothesis had stimulated the development of most of the classes of antidepressants that are now available. Examples of the 8 classes of antidepressants are shown in tables 1 and 2.

Of the novel antidepressants that have recently been introduced, agomelatine is unique due to its agonist action on the M1 and M2 melatonin receptors combined with its antagonistic action on 5HT2C receptors[3]. As a disturbance of the circadian rhythm (body temperature, sleep pattern, mood state, etc.) is a characteristic feature of major depression[4], the combination of an action on both melatonin and 5HT2C receptors gives agomelatine a unique pharmacological profile. Whether this will be reflected in its therapeutic activity remains to be seen.

Table 1	Currently available antidepressants 1
Tricyclics (TCA's)-amitriptyline, imipramine, clomipramine, dothiepin, desipramine, nortriptyline, maprotiline	
Non-selective monoamine oxidase inhibitors (MAOI's)-phenalzine, tranylcypromine, pargyline	
Reversible MAOI's (RIMA's)-moclobemide	
Serotonin and noradrenaline reuptake inhibitors (SNRI's)-venlafaxine, duloxetine, milnacipran	

Despite the advances that have been made over the past 50 years in improving the safety and tolerability of antidepressants, there has been little improvement in the therapeutic efficacy of these drugs. Some of the limitations of the currently available antidepressants are listed in table 3.

FUTURE DEVELOPMENTS OF ANTIDEPRESSANTS

Several hypotheses have been advanced to explain the delay in onset of the antidepressant response. Some 30 years ago, it was shown that the decrease in the density of post synaptic

Table 2	Currently available antidepressants 2
Selective serotonin reuptake inhibitors (SSRI's)-escitaloprom, citalopram, fluoxetine, fluvoxamine, sertraline, paroxetine	
Noradrenaline reuptake inhibitors (NRI's)-reboxetine	
Noradrenaline and serotonin specific antidepressants (NaSSA's)-mirtazepine, mianserin	
Other-bupropion, tianeptine, trazodone*, agomelatine	
* 5HT2C antagonist/M1 + M2 agonist.	

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Table 3	Limitations of currently available antidepressants

Side effects that reduce compliance
Drug interactions
Speed of therapeutic response, but is this a realistic target?
Antidepressants do not improve long-term cognitive deficits in severely depressed
Antidepressants may not protect against progression to dementia in the elderly
Are antidepressants limited as neuroprotective agents?

adrenoceptors following chronic antidepressant treatment was correlated with the onset of action of most classes of antidepressants .Since that time, it has also been reported that the deceased uptake of 3H-5HT into platelets from depressed patients was reversed by clinically effective antidepressant treatment[5], while more recently it has been demonstrated that different types of antidepressants increase the density of dopamine D2 and D3 receptors in the nucleus accumbens of rodents[6]. Thus adaptive changes in monoamine receptors appear to correlate with the time of onset of the therapeutic response.

However, there is now clinical evidence that the delay in response to antidepressant treatment may be a reflection of the pharmacological properties of the antidepressants that are available rather than an intrinsic property of all antidepressant treatments. Thus the N-methyl-D-aspartate (NMDA) glutamate channel antagonist ketamine has been shown to have an acute antidepressant effect that persists for several days after the drug has been administered[7]. The results of experimental studies demonstrate that the activation of the NMDA receptors leads to an increase in nitric oxide synthase (NOS) whereas conversely a reduction in NMDA receptor function ha the opposite effect. As NOS inhibitors have antidepressant-like effects in animal models of depression, it seems possible that the ketamine effect is mediated, at least in part, by a reduction in brain nitric oxide[8].

Besides these changes in neurotransmitter function that are associated with the onset synaptic plasticity associated with depression, changes that are partially reversed by effective antidepressant treatments. In addition, several investigators have shown that there is a dysfunctional intraneuronal signalling system in depression as reflected by the aberrant interaction between the adenylate and phospholipase C systems[9]. All antidepressants in current use have been shown to increase the synthesis of either cyclic adenosine monophosphate (cAMP) or phosphatidyl inositol (PI). Such changes result in the increased phosphorylation of cAMP-response element binding protein (CREB). The final pathway in this signalling cascade involves the activation of the brain derived neurotrophic factor (BDNF) gene, and the anti-apoptotic Bcl 2 gene, that results in increased neuronal repair and survival. In depression, the synthesis of BDNF is known to be reduced, a situation that is reversed following effective antidepressant treatment. Thus, by increasing neurotrophic factor synthesis, antidepressants enhance neuronal survival and neurogenesis. The possible pathways involved in antidepressant induced increase in the signalling cascade are shown in figure 1[10].

DEPRESSION, NEURODEGENERATION AND THE ACTION OF ANTIDEPRESSANTS

There is increasing evidence that chronic depression is ultimately associated with neurodegeneration. This neurode-

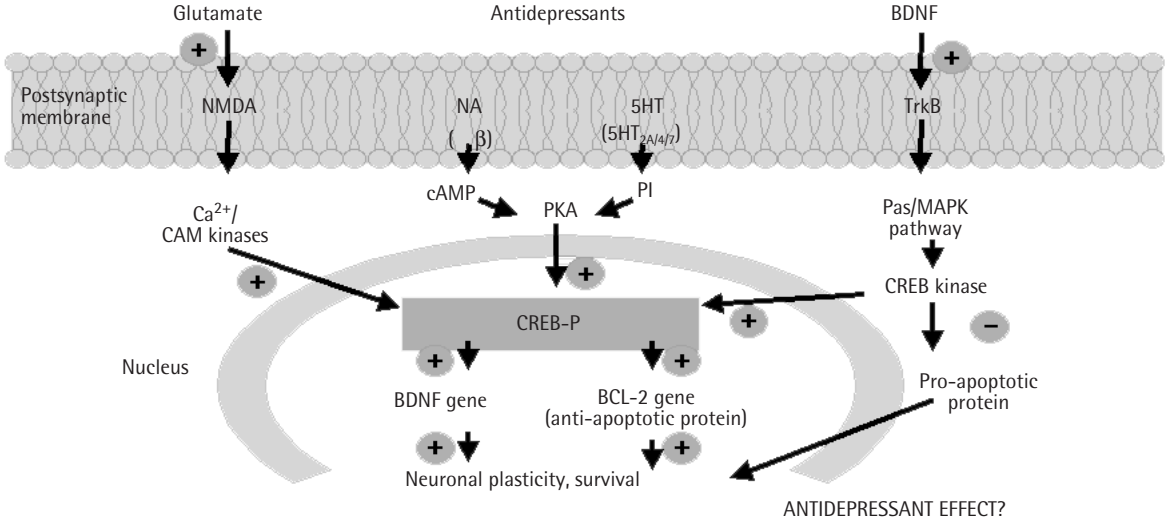

Figura 1 *Antidepressants, neurotrophic factors and neurogenesis: the final common pathway? TrkB: troponin receptor kinase pathway; CREB: cAMP response element binding protein; MAPK: neurotrophin-mitogen activating protein kinase. Adapted from D'Sa and Duman, 2002.*

generative hypothesis is supported by neuroimaging studies that indicate atrophy of the hippocampus, amygdalae and frontal cortex[11]]. The increased neurodegenerative changes are associated with a rise in the brain concentration of glucocorticoids, that are responsible for the reduction in the synthesis of neurotrophic factors such as BDNF (REF). In addition, the rise in pro-inflammatory cytokines (such as interleulins (IL) 1,-6 ,tumour necrosis factor alpha and interferon alpha), not only stimulate the hypothalamic pituitary-adrenal (HPA) axis to further increase the synthesis and secretion of glucocorticoids but also to increase the synthesis of prostaglandin E2 and nitric oxide in the brain[12].

Recent studies by Myint and coworkers[13] have extended the neurodegenerative hypothesis by implicating the role of the NMDA agonist quinolinic acid as a factor that contributes to neuronal degeneration. There is evidence that tryptophan, when metabolised through the kynurenine pathway by tryptophan and indoleamine dioxygenase (TDO and IDO), not only leads to a decrease in brain serotonin synthesis but also to an increase in the synthesis of quinolinic acid. This pathway is increased by pro-inflammatory cytokines. In depression, it is known that the neurodegenerative arm of the kynurenine pathway is increased thereby leading to the synthesis of the NMDA receptor agonist quinolinic acid. Although effective antidepressant treatment largely normalises the pro-inflammatory cytokines[14] and, by re-sensitising the central glucorticoid receptors, preliminary studies show that the neurodegenerative arm of the kynurenine pathway remains elevated despite clinical response to treatment. This highlights the need to develop a new generation of antidepressants that target the mechanisms directly involved in the inflammatory ad neurodegenerative changes in the brain[12].

NOVEL ANTIDEPRESSANTS IN DEVELOPMENT THAT APPEAR TO ACT VIA NON-AMINERGIC MECHANISMS

The following summarises some of the novel compounds that are at varying stages of clinical development:

- Combined inhibitors of tryptophan dioxygenase and the serotonin transporter (eg. 680C91). Such compounds have been shown in experimental studies to increase brain tryptophan concentrations by inhibiting the kynurenine pathway and enhancing serotonin function by inhibiting the reuptake transporter[15].
- The neuroendocrine hypothesis of depression postulates that depression arises as a consequence of the increase in glucocorticoids that desensitise glucocorticoid type 2 receptors thereby reducing the normal feed-back inhibition on corticotrophin factor release[16]. Chronic stress results in similar changes in the activity of the HPA axis. The neuroendocrine hypothesis postulates that the changes in central neurotransmitter function, and decrease in neuronal repair mechanisms that accompany chronic depression, are a consequence of the hypercortisolaemia. In support of this hypothesis, it has been shown that glucocorticoid antagonists, whether they inhibit the synthesis of these steroids or block the glucocorticoid receptors (for example, metapyrone, ketoconazole, mifipristone), demonstrate antidepressant activity in preliminary clinical trials.
- Anti-inflammatory drugs that are sufficiently lipophilic to penetrate the brain may offer a new approach to antidepressant treatments. There is clinical evidence that celecoxib, a cyclo-oxygenase 2 inhibitor widely used in the treatment of rheumatoid arthritis, has antidepressant properties in both experimental animals and in preliminary clinical trials[17]. There is also circumstantial evidence that drugs immunomodulating drugs that attenuate pro-inflammatory cytokines have potential antidepressant activity.
- Other novel approaches include the use of glycogen synthase kinase inhibitors (GSK-3). Such drugs are known to enhance neurogenesis and decrease apoptosis in the rodent brain and to have antidepressant-like effects. Lithium is a specific inhibitor of GSK-3 and is a valuable adjunct to antidepressants in patients who do not respond to antidepressant monotherapy.
- A decrease in the activity of the NMDA glutamate receptors, and an increase in a proportion of the metabotropic glutamate receptors, is associated with an enhancement of the activity of SSRI antidepressants. As has already been mentioned, the NMDA antagonist ketamine has antidepressant activity after acute administration. Thus anew generation of antidepressants may be developed based on the drugs that combine an antagonistic action on NMDA receptors with and agonistic action on m glutamate type 2 and 3 receptors.

CONCLUSIONS

Depression is a genetically based disorder that affects the whole body. The pathological changes that occur in depression are consequences of a dysfunctional endocrine, immune and neurotransmitter systems. To date, antidepressants have been developed based on the assumption that the monoamines are the primary cause of the disorder. However, it is now apparent that antidepressants reduce the hypersecretion of cortisol, reduce the release of pro-inflammatory cytokines, reduce the activities of cyclo-oxygenase 2 and nitric oxide synthase thereby decreasing the concentrations of inflammatory mediators in the brain, and reducing the activity of indoleamine dioxygenase thereby decreasing the concentration of the neurotoxin quinolinic acid. All these changes occur following chronic drug administration and approximately correlate with the time of onset of the antidepressant response.

In future, the discovery of novel antidepressants may be based on a deeper understanding of the pathological basis of depression by primarily targeting non-monoaminergic mechanisms.

REFERENCES

1. Schildkraut JJ. The catecholamine hypothesis of affective disorders; a review of supporting evidence. Am J Psychiat 1965; 122:509-22.
2. Coppen A, Prange AJ, Hill C. Abnormailities in indoleamines in affective disorders. Arch Gen Psychiat 1972;26:474-8.
3. Leonard BE. Melatonin receptors and antidepressant strategies. Ir J Psychiat 1997;8:37-40.
4. Wirz-Justice A, Krauchi K, Morimasa T. Circadian rhythm of tritiated imipramine bunding in rat suprachiasmatic nuclei. Eur J Pharmacol 1983;87:331-3.
5. Healy D,Carney PA, O'Halloran A, Leonard BE. Peripheral adrenoceptors and serotonin receptors in depression: changes associated with response to treatment with trazodone or amitriptyline. J Affect Dis 1985;285-96.
6. Lammers CH, Díaz J, Schwartz JC. Selective increase in dopamine D3 receptor gene expression as a common effect of chronic antidepressant treatments. Mol Psychiat 2000;5:378-88.
7. Berman RM, Cappiello A, Anand A. Antidepressant effects of ketamine in depressed patients. Biol Psychiat 2000;47:351-4.
8. Harkin AJ, Bruce KH, Craft B. Nitric oxide synthase inhibitors have antidepressant properties in mice: 1) acute treatments are active in the forced swim test. Eur J Pharmacol 1999;372:207-13.
9. Wachtel H. The second messenger dysbalance hypothesis of affective disorders. Pharmacopsychiat 1990;23:27-32.
10. Duman RS, Henninger GR, Nessler EJ. A molecular and cellular theory of depression. Arch Gen Pschiat 1997;54:597-608.
11. Sheline YI, Wang PW, Gado MH. Hippocampal atrophy in recurrent major depression. Proc Nat Acad Sci USA 1996;93:3908-13.
12. Leonard BE, Myint A-M. Inflammation and depression: is there a connection with dementia? Neurotox Res 2006;10:149-60.
13. Myint A-M, Kim Y-K, Verkerk R. Kynurenine pathway in major depression: evidence of impaired neuroprotection. J Affect Dis 2007;98:143-56.
14. Myint A-M, Leonard BE, Steinbusch HW. Th1, Th2 and Th3 cytokine alterations in major depression. J Affect Dis 2005;88:169-73.
15. Salter M. Selective inhibitor of tryptophan 2,3 dioxygenase and combined inhibitor of tryptophan 2,3 dioxygenase and serotonin reuptake as novel serotonergic antidepressants. CNS Drug Reviews 1996;2:127-43.
16. Gold PW, Goodwin FK, Chrousos GP. Clinical and biochemical manifestations of depression: relation to the nerobiology of stress. Pts 1&2. N Engl J Med 1988;319:348-53 and 413-20.
17. Mueller N, Schwartz MJ, Dehning S. The cyclo-oxygenase 2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomised, placebo controlled, add-on pilot study to reboxetine. Mol Psychiat 2006;11:680-68.