Inflammation, Insulin Resistance and the Pathophysiology of Depression: Implications for Novel Antidepressant Developments

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Abstract

This review summarises the impact of chronic low grade inflammation as a causative factor in the pathophysiology of major depression. Evidence is presented to show that proinflammatory cytokines both directly, and indirectly by increasing hypercortisolaemia, desensitise insulin receptors and thereby decrease the transport of glucose into the brain (the diabetic brain). In addition, the proinflammatory cytokines activate the tryptophan-kynurenine pathway which results in the synthesis of the NMDA-glutamate receptor agonist quinolinic acid. This acts as a neurotoxin and facilitates neuronal apoptosis. As metabolic changes initiated by low grade inflammation underlie the pathophysiology of depression, drugs which attenuate the inflammatory cascade may present an approach to the novel development of antidepressants. The review concludes with a summary of drugs which might be considered for their novel therapeutic activity.

Key points are;

i) Chronic low grade inflammation commonly occurs in major depression and contributes to adverse changes in brain energy metabolism by decreasing insulin receptor function and thereby reducing glucose transport into the brain. ii) Low grade inflammation initiates an increase in the tryptophan-kynurenine pathway which enhances the NMDA-glutamate receptor function and thereby increases neuronal apoptosis, iii) As many of the pathophysiological changes in depression result from dysfunctional brain metabolism caused by chronic low grade inflammation, it is concluded that drugs targeting the inflammatory pathways may offer new possibilities for the development of novel antidepressants.

INTRODUCTION

In recent years there has been more attention directed towards a more holistic view of depression in which the immune and endocrine systems play a significant role. The potential importance of the immune system in the pathology of major depression led Smith, in 1991, to formulate the macrophage theory of depression \cite{1} in which he summarised the clinical evidence of inflammation due to the overactivity of peripheral and central macrophages as an important causal factor. Since then, evidence has accumulated to indicate that chronic low grade inflammation is an important contributor to the pathophysiology of depression \cite{2}. For example, Dowlati and colleagues \cite{3}, in a detailed meta-analysis of raised proinflammatory cytokines in major depression, confirmed that interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) were consistently raised. These proinflammatory cytokines are raised in response to stress and have been demonstrated to occur in other major psychiatric disorders such as schizophrenia, bipolar disorder and the anxiety disorders \cite{4,5,6}. In addition to the proinflammatory cytokines, prostaglandin E2 (PGE2), reactive oxygen species and lipid peroxidation also increase in depression in response to stress. Thus proinflammatory cytokines can interact with virtually all pathophysiological changes that characterise major depression and thereby influence neurotransmitter function, synaptic plasticity and ultimately neuronal structure. This could result in increased apoptosis and contribute to dementia in later life (Figure 1).

2. The link between inflammation and insulin resistance

Inflammation has emerged as a major pathophysiological link between major depression and the metabolic syndrome \cite{7}. Both conditions, irrespective of the underlying psychiatric disorder, are characterised by an increase in proinflammatory cytokines and the development of insulin and glucocorticoid receptor resistance. While it may appear to be contradictory that stress induced hypercortisolaemia...
co-exists with elevated proinflammatory cytokines, in depression and in chronic stressful situations the peripheral and central glucocorticoid receptors become insensitive due to the internalisation for the receptors from the cell surfaces, changes which arise from the excessive activation of the receptors by the elevated glucocorticoids [8].

Functional insulin insensitivity arises as a consequence of the glucocorticoids decreasing the insulin mediated expression of the glucose transporter GLUT4. This results in a reduction in the transport of glucose into both peripheral and, most importantly, the brain [9]. Further changes in insulin receptor signalling arise due to the cortisol induced release of fatty acids from cellular lipoproteins while the increased proinflammatory cytokines also directly contribute to the desensitisation of the insulin receptors [10].

These adverse changes in the insulin receptor signalling are usually offset by the activity of the adipokine, adiponectin, which can reactivate the desensitised receptor. However, the concentration of adiponectin is decreased in depression and as a consequence of the metabolic syndrome thereby compounding the reduction in insulin receptor function [11]. Thus the key metabolic changes initiated by hypercortisolaemia and chronic low grade inflammation are instrumental in causing insulin receptor dysfunction. As a consequence, glucose transport is impeded which would have a significant impact on brain glucose metabolism.

3. The contribution of the tryptophan-kynurenine pathway to decreased insulin receptor function.

In recent years there has been a renewed interest in the role of the tryptophan-kynurenine pathway in depression. In depression, the free plasma tryptophan concentration is decreased thereby reducing its availability for the synthesis of serotonin. This effect is linked to the increase in the metabolism of tryptophan by proinflammatory cytokine activated indoleamine 2,3 dioxygenase, located in the brain and many peripheral tissues, and by tryptophan dioxygenase which is activated by glucocorticoids and located in the liver. In depression, and under stressful situations, these enzymes are activated and result in the metabolism of tryptophan to kynurenine and kynurenine metabolites [12,13]. Kynurenine is a substrate for both kynureninase and kynurenine aminotransferase. In depression the former enzyme is activated leading to the formation of quinolinic acid, an agonist at N-methyl-D-aspartate (NMDA) glutamate receptors, and the diabetogenic kynurenine metabolites anthranilic acid and 3-hydroxyanthranilic acid. By reducing the activity of insulin, these substrates further contribute to the reduction in the availability of glucose for sustaining brain metabolism [14,15]. This neurodegenerative, diabetogenic pathway is normally balanced under non-stress conditions by the synthesis of the NMDA glutamate agonist, kynurenic acid, which is formed by the action of kynurenine aminotransferase. This neuroprotective pathway is decreased in depression while the neurodegenerative arm of the tryptophan-kynurenine pathway is increased [13].

However, in depression a chronic decrease in high energy substrates resulting from a deficit in glucose and essential cofactors in depression may also be of importance in causing the increase in neuronal apoptosis [16]. The situation is further complicated by the increase in oxygen free radicals caused by xanthenuric acid and 3-hydroxykynurenine which damage the mitochondrial membranes thereby resulting in a reduction in the synthesis of adenosine triphosphate and other high energy intermediates [17] (Figure 2).
4. Inflammation, insulin insensitivity and reduced brain energy metabolism in depression: could the link provide a guide for the development of novel antidepressants?

The search for novel psychotropic drugs has, with few exceptions, largely depended on the extension of currently available drugs into areas for which they were not initially developed. For example, many second generation antipsychotics are now used as adjunctive treatments for therapy resistant depression or even in some cases such as quetiapine as a single agent for treating depression. Anti-convulsants have been used for several decades to treat bipolar disorder while the SSRI antidepressants are widely used to treat anxiety disorders and pain syndromes. Clearly the classification of psychotropic drugs according to the therapeutic category of their clinical use (antidepressants, antipsychotics, anti-manic etc) is becoming increasingly meaningless as the complexity in the understanding of their pharmacology becomes apparent. This situation has led to the establishment of new classification guidelines by the “Neuroscience based Nomenclature Committee” which was established recently with representatives from the main world neuropsychopharmacological societies under the chairmanship of Zohar [18].

However, despite the therapeutic benefits that have arisen from the extension of the newer psychotropic drugs there is no evidence that they are significantly improved on their predecessors. Perhaps it is timely to consider an approach based on drugs which act as anti-inflammatory agents.

4a. Anti-inflammatory drugs as potential antidepressants

In addition to the proinflammatory cytokines, prostaglandin E2 (PGE2) is also increased in the blood and cerebrospinal fluid of patients with major depression [19]. As inflammation, commonly associated with arthritis and other inflammatory disorders, is attenuated by treatment with non steroidal anti-inflammatory drugs (NSAID’s) it is reasonable to expect such drugs to alleviate the impact of chronic low grade inflammation associated with depression and other psychiatric disorders in which inflammation contributes.

Of the NSAID’s available, aspirin is still the most widely used largely on grounds of efficacy and cost. However, the adverse effects of long term use are well known and attributed to the inhibition of the synthesis of PGE2 by cyclooxygenase-1 in the wall of the gastric mucosa. For this reason, a new generation of NSAID’s have been developed that selectively inhibit cyclooxygenase-2, an enzyme that is induced by inflammatory cytokines acting on neurons particularly in the hippocampus and cortex [20]. On theoretical grounds, a centrally acting COX-2 inhibitor should enable the inflammation hypothesis of depression to be tested as the inhibition of COX-2 should result in the reduction of PGE2 synthesis, particularly in the brain. Experimental studies have demonstrated that the selective COX-2 inhibitor celecoxib reduces the stress response and cognitive deficits in the rat [21] and also the behavioural and immune changes in the olfactory bulbectomised rat model of depression [22].

In clinical studies, (open and randomised, double-blind trials) there are positive results to demonstrate that celecoxib enhances the response of antidepressants (fluoxetine, reboxetine, sertraline and mood stabilisers) given concurrently [23,24,25,26]. There is also an “open” study showing that aspirin enhances the antidepressant effects of fluoxetine [27].

Adjunctive treatment of celecoxib with an antidepressant has also been shown to be beneficial in patients with bipolar disorder. Thus Nery and coworkers [28] showed that celecoxib treatment produced a rapid onset antidepressant response and similar findings have been reported by Halaris et al (in preparation) in a group of treatment resistant bipolar patients given escitalopram and celecoxib. A
meta-analysis of the efficacy of adjunctive celecoxib treatment for patients with major depression showed that the combined treatment resulted in better remission and response rates compared to those receiving the antidepressant plus a placebo [29]. A recent meta-analysis by Koehler and coworkers [20] supported this conclusion. Despite the appeal of these clinical results, it must be emphasised that the potential links between inflammation and depression are highly complex and the results of the clinical trials are so far limited [30]. Not all studies have shown the beneficial effects of adjunctive celecoxib with SSRI antidepressants while Maes [31] has raised a number of questions regarding the theoretical limitations of PGE2 inhibitors. In addition to clinical and theoretical limitations there remains the risk of severe cardiovascular events which have been recognised for COX-2 inhibitors [32]. Thus as a precaution, the adjunctive treatment of antidepressants with celecoxib should be confined largely to younger patients with few depressive episodes and a low a priori risk of cardiovascular disease. Furthermore, it still remains to be demonstrated that selective COX-2 inhibitors given alone are safe and effective long-term treatments for depression without causing major adverse central and peripheral side effects [31].

4b. Drugs which target insulin and glucose transporters

As insulin resistance appears to play a crucial role in the metabolic changes associated with major depression it is timely to consider if the insulin receptor could provide a target for the development of novel antidepressants. This seems particularly pertinent as the adverse changes in insulin function are triggered by inflammation and hypercortisolaemia which frequently accompany depression.

Insulin plays such a crucial role in brain metabolism and insulin resistance is a critical feature of major depression it would be anticipated that the administration of insulin might reverse the consequences of insulin resistance. There is evidence that patients with major depression and Alzheimer’s disease have a reduced insulin receptor sensitivity [33]. In addition, particularly those patients with Alzheimer’s disease have a hypophosphorylation of the insulin receptor and the insulin receptor substrate [34]. An increase in insulin signalling improves memory in cognitively normal healthy humans [35]. Thus it was shown that the intranasal administration of insulin over a period of 8 weeks improved the performance on a declarative memory task, an effect which primarily involved improved hippocampal function [35]. Furthermore, verbal memory, which depends on the activation of the frontal cortex, was shown to improve following the intranasal application of insulin [36]. While such studies have not yet been reported in patients with major depression, Freiherr and coworkers [36] have reviewed the studies on the use of intranasal insulin in the treatment and prevention of Alzheimer’s disease and concluded that strategies for enhancing insulin signalling could also be beneficial in reducing the transition from depression to dementia. However, such beneficial effects depend on the absence of Apo E 4 carrier status. Thus Rosenbloom and colleagues [37], in a single dose pilot trial of intranasal rapid-acting insulin in Apo E4 carriers with mild to moderate Alzheimer’s disease, found that insulin failed to have an effect on memory performance. These preliminary results, if replicated in a larger cohort of patients, suggest that intranasal insulin, or drugs such as tiraglutide which sensitise insulin receptors, may be beneficial for subgroups of depressed or demented patients who lack the ApoE4 genotype.

At present, it is uncertain whether intranasal insulin could have a beneficial effect in correcting the adverse metabolic changes which also characterise major depression. However, there is experimental evidence that insulin-like growth factor increases hippocampal neurogenesis and insulin signalling within the brain; it has also been shown to exhibit antidepressant-like activity in rodent models of depression [38]. Clearly it is now important to consider if these preliminary experimental and clinical observations can be translated into therapeutic strategies for the treatment of major depression.

In addition to the direct application of insulin, one obvious area to explore is the role of anti-diabetic drugs and their effects on brain function. Of the numerous types of orally active drugs used for the treatment of type 2 diabetes (DM2), metformin is one of the most intensively used for a first line oral therapy.

The mode of action of metformin depends on the cellular ratio of AMP/ATP. The reduction in the peripheral glucose level occurs due to the inhibition of liver gluconeogenesis and a reduction in available glycogen. Metformin also inhibits mitochondrial function resulting in defective cyclic AMP synthesis and protein kinase signalling. There is also evidence that metformin increases the sensitivity of insulin receptors and stimulates AMP-activated protein kinase [39].

Metformin is lipophilic and therefore has easy access to the brain. In vitro studies have demonstrated that metformin can prevent the formation of beta amyloid plaques and the hyperphosphorylation of tau protein [40], both of which are increased in the brain of elderly depressed patients but of greater density in those with dementia. Experimentally it has also been shown that metformin increases neurogenesis and reduces the effects of oxidative stress [41]. However, treatment with metformin did not counteract experimentally induced cognitive decline even though it attenuated insulin resistance and reduced the impact of a high fat diet on the increase in body weight [42].

4c. Polyunsaturated fatty acids as complimentary treatment for major depression

Polyunsaturated fatty acids, also known as essential fatty acids, are important components of membrane structures and essential for the development and function of the
central nervous system. These are long chain fatty acids and the two types which are of major importance for brain function are eicosapentenoic and docosahexanoeic acids. These fatty acids are classified as n-3 or omega-3 fatty acids as the carbon chain contains 3 unsaturated double bonds. In addition to their role in membrane structure, the n-3 fatty acids are also involved in the maintenance of membrane fluidity, gene expression and in neuronal development [43]. As there is both experimental and clinical evidence that the n-3 fatty acids have anti-inflammatory properties [44] there has been considerable interest in exploring the effects of diets rich in these fatty acids and in determining if their deficiency is associated with cognitive and affective changes [45,46].

A deficiency of n-3 fatty acids associated with chronic inflammatory diseases such as cardiovascular disease and autoimmune disease which often coexist with major depression [48].

In contrast to the n-3 fatty acids which are anti-inflammatory, the long chain n-6 fatty acids, such as linolenic acid, are pro-inflammatory in their action [43]. The structural difference between the n-3 and n-6 fatty acids lies in the location of the double bonds in the carbon skeleton. The n-6 fatty acids can act as antagonists to the n-3 fatty acids. As both the n-3 and n-6 fatty acids are essential components of neuronal membranes, dietary or disease initiated changes in their membrane composition can have a profound effect on neuronal, glial and immune function [47].

The dietary importance of the n-3 and n-6 fatty acids has been the focus of important epidemiological studies. Populations with a high intake of n-3 fatty acids (fatty fish for example) have a lower frequency of chronic inflammatory and cardiovascular disease and a slower rate of cognitive decline in old age than those populations with a poor n-3 fatty acid diet [49]. Thus as the ratio of the n-3: n-6 fatty acids have decreased due to the increasing consumption of grain based diets, not only has the frequency of inflammation linked diseases increased but the frequency of depression in later life has also increased [50,51]. However, supplementation of the diet with n-3 fatty acids has so far had a disappointing outcome and the therapeutic benefits of n-3 fatty acids in patients with inflammatory disorders remains doubtful [51].

Despite the largely negative results of the dietary supplementation studies experimental studies have shown that the supplementation of the diet of rats with the polyunsaturated omega-3 (n-3) fatty acid can normalise changes in the inflammatory state and reduce the stress induced hyperactivity of the HPA axis [52,53]. The result of such studies support the view that n-3 fatty acids might be useful in the adjunctive treatment for major depression.

Clinical studies have shown that a dietary deficiency in n-3 fatty acids is associated with a higher frequency of major depression [54,55]. In addition, the extent of the reduction in the concentration of n-3 fatty acids in erythrocyte membranes reflects the frequency of previous depressive episodes in elderly patients [57].

Despite the limitations of the clinical studies, the results do suggest that there is a sub-population of depressed patients who may benefit from n-3 fatty acids given concurrently with the usual antidepressant medication. There is also a suggestion from the clinical studies that such treatments may be beneficial in treating the early stages of cognitive decline in elderly depressed patients.

4d. The role of polyamines as modulators of inflammation and neurodegeneration

Agmatine and spermidine are examples of endogenous polyamines found in mammals. Of these, agmatine is synthesised from the amino acid arginine by arginase decarboxylase. It is widely distributed in mammals and is specifically transported into neurons by a cationic amino acid transporter. In the brain, agmatine is further metabolised by nitric oxide synthase to nitric oxide and by a separate pathway to spermidine and spermine [58]. Thus agmatine is important in the brain as a source of nitric oxide and the polyamines spermidine and spermine, in addition to its possible neurotransmitter function and ability to interact with other neurotransmitter pathways [59].

From the therapeutic perspective, agmatine is of potential importance because experimentally it has been demonstrated that it has antidepressant, anti-anxiety, and cognitive enhancing properties which reflect its broad neuroregulatory effects by modulating neurotrophic pathways [60]. Agmatine dose dependently reduces the deficits in memory and learning induced in rodents by scopolamine [61]. It has been also shown that agmatine might have modulatory effect of on cognitive functions during vascular dementia through eNOS and BDNF expression [62]. At the cellular level, agmatine has a high affinity for alpha 2 receptors and
4e. Some miscellaneous drugs and compounds which have immunomodulating properties

Monoclonal antibodies as putative antidepressants: There is experimental and clinical evidence to suggest that antibodies to the proinflammatory cytokines such as TNF-alpha, which are raised in depression and chronic inflammatory disorders such as psoriasis and rheumatoid arthritis, can attenuate not only the symptoms associated with joint pain and skin lesions but also reduce the symptoms of fatigue and depression which are frequently associated with inflammatory disorders. Of the clinical trials which support the evidence that monoclonal antibodies have potential antidepressant activity associated with the reduction in inflammation, etanercept [74], infliximab [75] and adalimumab [76] have been noted for their activity in reducing the depressive symptoms concurrently with the reduction in the inflammatory cytokines. Of the clinical studies cited, that by Raison and colleagues [75] is particularly pertinent as it indicated that the anti-TNF alpha monoclonal antibody infliximab produced a positive antidepressant response in a group of patients with therapy resistant depression. Apart from the unacceptably high cost of monoclonal antibody therapy, these results indicate that direct immunomodulation of proinflammatory cytokines is worthy of consideration when developing a new generation of antidepressants.

Minocycline, an antibiotic with anti-inflammatory properties: Minocycline is a tetracycline antibiotic that crosses the blood-brain barrier and has shown both anti-inflammatory and anti-oxidant effects in experimental and clinical studies [77]. Experimentally minocycline has been shown to increase neurogenesis, reduce the release of proinflammatory cytokines from activated microglia and to have anti-inflammatory activity. It inhibits the activation, migration and/or proliferation of T-cells, neutrophils and microglia and inhibits the release of proinflammatory cytokines. The anti-inflammatory effects of minocycline, which have been reported experimentally and clinically, are independent of its antibiotic properties [78].

Over 20 years ago there was a suggestion in the clinical literature that minocycline may have an antidepressant profile [79]. Later, in an open label study, minocycline was shown to have antidepressant effects in a group of patients with unipolar psychotic depression [80]. A double-blind, placebo controlled, randomised trial of minocycline for mild to moderate depression in HIV patients demonstrated antidepressant effects [81] while in a major clinical trial in bipolar disorder, it was concluded that while there was no significant effect of the drug on the MADRS sores across the treatment period, minocycline may be an efficacious adjunctive treatment for bipolar depression [82]. From these preliminary clinical results it may be concluded that minocycline is worth consideration as an adjunctive treatment for depression, particularly in the subgroup of patients in which proinflammatory changes are apparent.
The statins for the adjunctive treatment of depression: The statins are a group of HMG-CoA reductase inhibitors which are widely used to reduce high cholesterol levels and thereby prevent serious cardiovascular events. In addition to their effects on cholesterol metabolism, statins have anti-inflammatory effects and have been used successfully as adjunctive treatments for major depression [83]. A meta-analysis has indicated that statins are effective in enhancing the antidepressant efficacy of different types of antidepressants [84].

However, in recent years concerns have been raised regarding the side effects of the statins, in particular the increase in irritability, anxiety and depression [85]. The cause of these side effects is still uncertain but it is known that cholesterol plays a significant role in neuroprotection and that low cholesterol levels impact on serotonin receptor function [86]. The reduction in cholesterol by statins has been shown experimentally to affect the function of 5HT1A [87] and 5HT7 [88] receptors. However, the causal relationship between the use of statins and the frequency of depressive symptoms is unclear. The statins affect the activity of cytochrome P 2C9 which could impact on the efficacy of antidepressants such as sertraline and fluvoxamine. In addition, the high density lipoprotein fraction of cholesterol (“good” cholesterol) is lower in patients with major depression [90] so that a further reduction in the concentration by a statin could have major adverse consequences. While there may be a use for statins as adjunctive treatments for depression in the future, based on the current clinical evidence it would appear that other approaches to the development of novel antidepressants, already discussed above, deserve priority consideration.

5. CONCLUSION

The purpose of this review was to consider some of the major metabolically related changes in major depression which could provide novel targets for psychotropic drugs. As these targets ultimately involve changes in brain energy metabolism, it is reasoned that the restoration of normal brain metabolic activity will be reflected in an improvement in depression. As chronic low grade inflammation appears to play a crucial role in the pathophysiology of major depression, the primary target for novel antidepressants is the inflammatory mediators and their cellular origins. A more direct target affecting brain metabolism is the insulin receptor and the glucose transporter mechanisms associated with the receptor. Some of the approaches, and their targets, mentioned in this review are shown in Figure 3.
While these approaches do not directly involve targeting specific neurotransmitters, it is certain that any changes leading to the improvement in brain energy metabolism will have an impact on most other cellular pathways. Major depression, like all other major psychiatric disorders affects the whole body and a fundamental improvement in brain energy metabolism could provide a useful target for drug development.

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