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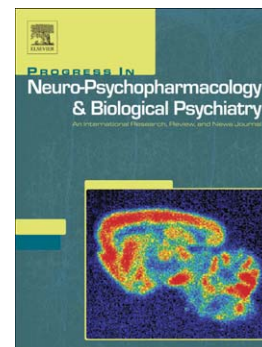
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Putative neuroprotective agents in neuropsychiatric disorders

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Abstract

In many individuals with major neuropsychiatric disorders including depression, bipolar disorder and schizophrenia, their disease characteristics are consistent with a neuroprogressive illness. This includes progressive structural brain changes, cognitive and functional decline, poorer treatment response and an increasing vulnerability to relapse with chronicity. The underlying molecular mechanisms of neuroprogression are thought to include neurotrophins and regulation of neurogenesis and apoptosis, neurotransmitters, inflammatory, oxidative and nitrosative stress, mitochondrial dysfunction, cortisol and the hypothalamic-pituitary-adrenal axis, and epigenetic influences. Knowledge of the involvement of each of these pathways implies that specific agents that act on some or multiple of these pathways may thus block this cascade and have neuroprotective properties. This paper reviews the potential of the most promising of these agents, including lithium and other known psychotropics, aspirin, minocycline, statins, N-acetylcysteine, leptin and melatonin. These agents are putative neuroprotective agents for schizophrenia and mood disorders.

List of Abbreviations:

IO&NS	inflammatory, oxidative and nitrosative stress
CSPT	cortico-striatal-pallidal-thalamic
IL	interleukin
TNF- α	tumour necrosis factor – alpha

TRYCAT	tryptophan-catabolite
IFN- γ	interferon-gamma
Apo-E	Apolipoprotein-E
NAC	N-acetylcysteine
ERK	extracellular signal-regulated kinase
MAP	mitogen-activated protein kinase
NO	nitric oxide
GSK-3 β	glycogen synthase kinase 3 β
BDNF	Brain derived neurotrophic factor
GDNF	Glial cell line-derived neurotrophic factor
IP-10	IFN- γ -inducible protein-10
CC16	Clara cell protein or uteroglobulin
sIL-1RA	soluble interleukin -1 receptor antagonist
PMA	phorbol 12-myristate 13-acetate
BAG-1	bcl-2 associated athanogene-1
EAE	experimental autoimmune encephalomyelitis
LIF-R	leukaemia inhibitory factor receptor
Bcl-2	apoptosis regulator protein
PANSS	Positive and Negative Symptoms Scale

PGE ₂	prostaglandin E2
COX-2	Cyclooxygenase-2
EPO	Erythropoietin
NAC	N-acetylcysteine
SCF	Stem cell factor
G-CSF	granulocyte-colony stimulating factor
HMG CoA	hydroxymethylglutamyl coenzyme A
TDO	tryptophan 2,3-dioxygenase
NAS	N-acetylserotonin
AANAT	arylalkylamine-N -acetyltransferase

1. Introduction

Many individuals with major neuropsychiatric disorders such as depression, bipolar disorder and schizophrenia demonstrate illness characteristics consistent with neuroprogression. These illness characteristics include progressive structural brain changes, cognitive and functional decline, poorer treatment response and an increasing vulnerability to relapse with chronicity. Alterations in the inflammatory and immune systems have been documented to occur from the earliest stages of schizophrenia, and have been associated with neurodevelopmental changes (Altamura et al., 2012). Many mental illnesses are associated with changes in brain morphometry, typically with reduced overall brain volume. In addition, different disorders demonstrate specific patterns of morphologic change. For example, major depression has been associated with volumetric abnormalities in cortico-striatal-pallidal-thalamic (CSPT) circuits (Bora et al., 2011d) and grey matter reductions in the rostral anterior cingulate cortex (Bora et al., 2011a). Bipolar disorder has been associated with grey matter reduction in the anterior limbic region (Bora et al., 2010) and ventricular enlargement (Strakowski et al., 2002). People with schizophrenia show greater dorsomedial and dorsolateral prefrontal cortex grey matter reductions compared to those with bipolar disorder (Bora et al., 2011b). Changes in brain morphometry have also been recorded in individuals with obsessive compulsive disorder (Fontenelle et al., 2009), post-traumatic stress disorder (Thomaes et al., 2010) and borderline personality disorder (Brunner et al., 2010). Morphometric changes may vary with gender (Bora et al., 2011c) and duration of illness (Takahashi et al., 2009). In schizophrenia and bipolar disorder, these changes are first evident in the ultra-high risk period, and are expressed by the first episode (Bechdolf et al.,

2012). This demonstrates that neurotoxic processes leading to morphological changes are occurring with major mental illnesses and suggest that these processes may commence prior to illness onset and continue with illness progression. Sanches et al (Sanches et al., 2008) reviewed evidence of changes in neurodevelopment in bipolar disorder and found strong evidence of premorbid neurobehavioural changes, especially attention impairment, as well as multiple neuroimaging differences between the children of bipolar parents and age-matched healthy controls.

Mechanisms that may drive these changes include oxidative and nitrosative stress (O&NS), activation of immuno-inflammatory pathways, dysfunction in mitochondrial pathways, apoptotic and neurotrophic factors (Berk et al., 2011b). These insights however unveil the possibility that by using agents to prevent activation of potentially neurotoxic pathways, we may be capable of instituting neuroprotective strategies that can reduce the incidence and impact of mental disorders. For example, agents that suppress inflammation and O&NS protect mitochondria (Carrasco-Pozo et al., 2012). Neurotrophic factors or compounds that have been found to prevent brain changes may have wider neuroprotective capabilities, with relevance to the treatment of psychiatric disorders. Their putative mechanisms of neuroprotective action are shown in Table 1. Numerous pharmaceutical and nutritional agents have been postulated as potential neuroprotective agents. These include currently used psychotropic agents pharmaceuticals currently indicated for non-psychiatric illnesses (e.g. immune-modulating agents) and nutraceuticals. These agents, including the most promising nutritional agents, may exert neuroprotective effects through anti-oxidative pathways, by shifting the redox balance, or bioenergetic pathways to enhance mitochondrial function.

Neuroprotective agents have received considerable attention for the treatment of neurological disorders, especially Alzheimer's, Parkinson's and ischemia/stroke. Many neuroprotective pathways may have a broad applicability across different neurodegenerative conditions. These include anti-apoptotic, neurotrophic, anti-inflammatory and immunosuppressant pathways. Biomarker changes have shown no respect to DSM-IV boundaries. Consequently, agents that regulate biomarkers that mediate changes in these broad pathways may be useful across numerous illness categories. Consequently research using a specific illness model may also be relevant to other illnesses. In contrast, narrow investigations of an agent's effect on specific insult models may provide limited insights into the neuroprotective properties of these agents in mental health. In this article, we review putative neuroprotective agents for schizophrenia and comorbid depression.

2. Neuroprogressive pathways in schizophrenia, depression and bipolar disorder

Schizophrenia is accompanied by neuroprogression (Menon et al., 1995, Anderson and Maes, 2012b), with changes evident as early as the prodromal or at-risk period (Pantelis et al., 2003). Further brain atrophy may also occur during acute exacerbations (Hulshoff Pol and Kahn, 2008). Numerous neuropathological pathways in schizophrenia may explain these neuroprogressive processes, including neuronal loss secondary to neuroinflammation (e.g. increased pro-inflammatory mediators including interleukin-1 (IL-1), tumor necrosis factor – alpha (TNF- α), interleukin-6 (IL-6)) and T helper cell -1like (e.g. interferon-gamma (IFN- γ) cytokines), increased O&NS processes and glutamate and tryptophan-catabolite (TRYCAT) levels (Anderson and Maes, 2012b, Anderson et al., 2012, Muller et al., 2011,

Wonodi and Schwarcz, 2010). Moreover, many genes that are known risk factors for dementia subtypes are also risk genes for schizophrenia (e.g. Neuroregulin-1, Apolipoprotein-E (Apo-E), Betasecretase-1, Notch, interleukin-18 (IL-18), fibroblast growth factor-1)(Anderson and Maes, 2012b). These risk genes may contribute to neuronal loss and altered synaptic plasticity.

As with schizophrenia, analogous processes occur in depression and bipolar disorder. BDNF is reduced in unmedicated patients with both depression (Yoshida et al., 2012) and bipolar disorder (Goldstein et al., 2011), and IO&NS markers are increased (Leonard and Maes, 2012). The BDNF Val66Met gene polymorphism has been associated with reduced brain volumes in schizophrenia (Agartz et al., 2006) and bipolar disorder (Teh et al., 2012) with conflicting evidence in major depression (Cole et al., 2011, Gonul et al., 2011). Depression has been associated with lowered antioxidant status and lowered antioxidant enzyme activity, which may lead to damage to fatty acids, proteins and DNA (Maes et al., 2011). Redox dysregulation is noted in all three disorders, including reduced glutathione defences and increased oxidative damage, indexed by changes such as lipid peroxidation (Gawryluk et al., 2011).

3.1 Antipsychotics and Cytokines

In this context it is noteworthy that many antipsychotics suppress ~~immune-~~inflammatory induction of pro-inflammatory cytokines and immune-inflammatory pathways (Drzyzga et al., 2006). In a recent meta-analysis involving 488 patients, antipsychotic treatment significantly increased levels of soluble interleukin-2 receptor and interleukin-12, and decreased levels of interleukin-1beta, IL-6 and transforming growth factor – beta (Miller et al., 2011). Two studies have shown a significant

correlation between levels of psychopathology and IL-6 at baseline (Frommberger et al., 1997, Pae et al., 2006), and treatment with antipsychotics resulted in a decrease in IL-6 levels that positively correlated with a reduced psychopathology score. However, it should be noted that heterogeneity in antipsychotic effects on cytokine levels has been shown in different schizophrenia patient studies (e.g. clozapine increased IL-6 levels (Maes et al., 1994) but quetiapine did not (Igue et al., 2011). Also clozapine has been shown to decrease enhanced baseline levels of IL-6 in another study after 6 months of treatment, concurrent to decreasing interleukin-2, interleukin-18 and TNF- α (Lu et al., 2004a). Changes in cytokine levels occurred within weeks of commencement on antipsychotics, with a significant decrease in IL-6 being evident within 9 days in one study (Frommberger et al., 1997). Risperidone, unlike haloperidol, modulates cytokine production by antigen presenting dendritic cells (Chen et al., 2012), enhancing interleukin-10, IL-6, interleukin-8 and TNF- α , but reducing IP-10 (IFN- γ -inducible protein-10) and interleukin-12. Risperidone also lowered IFN- γ production by T-cells. Although some heterogeneity is evident in the effects of antipsychotics, generally there is a normalization of levels shortly after treatment is commenced for acute exacerbations.

3.2 Antipsychotics, Autoimmunity and TRYCATs

Antipsychotics not only modulate the cytokine network but also impact neuroinflammation, TRYCAT production and myelination. There is also evidence that antipsychotics modulate microglia activation (Kato et al., 2008, Monji et al., 2011). Myint et al. (Myint et al., 2011) demonstrated that antipsychotics significantly decrease levels of neurotoxic TRYCATs, such as 3-OH-kynurenine, while increasing the levels of kynurenic acid, a neuroprotective TRYCAT. Antipsychotics also activate

Apo-E (Vik-Mo et al., 2009). Thus, antipsychotics may improve decreased levels of Apo-E, abnormalities in myelination and synaptic plasticity in schizophrenia (Garver et al., 2008, Dean et al., 2008). These results suggest that antipsychotics exert diverse effects on immuno-inflammatory and TRYCAT pathways, and are not restricted to direct effects on neurotransmitters systems. It should be noted that however that pro-inflammatory and cell mediated immune cytokines also interact to increase production of TRYCATs and decrease production of serotonin through activation of indoleamine 2,3-dioxygenase (Moylan et al., 2012), underpinning the interconnectedness of these systems.

4. Psychotropic agents

4.1 Lithium

Lithium has a strong evidence base supporting its ability to upregulate several neuroprotective pathways. Lithium upregulates the apoptosis regulator protein B cell lymphoma-2 (Bcl-2), inhibits glycogen synthase kinase 3 β (GSK-3 β) and induces brain derived neurotrophic factor (BDNF) in neuronal cultures (Chuang et al., 2011, Chalecka-Franaszek and Chuang, 1999). All these factors support a direct positive effect of lithium on brain growth factors and inhibition of apoptosis. Furthermore, lithium inhibits oxidative damage and increases glutathione in cultured rat cortex (Cui et al., 2007). There is also some evidence that lithium treatment of bipolar patients may be associated with changes in concentrations of pro-inflammatory cytokines interleukin-1-beta (IL-1 β) and IL-6 (Knijff et al., 2007). A magnetic resonance spectroscopy study of 21 volunteers administered lithium for four weeks demonstrated that lithium treatment was associated with an increase in brain N-acetylaspartate (Moore et al., 2000).

Lithium *in vitro* significantly increases the production of pro-inflammatory (e.g. IFN- γ , TNF- α , IL-8) and anti-inflammatory immunoregulatory cytokines / compounds (e.g. IL-10 and the IL-1 receptor antagonist) (Maes et al., 1999). Nevertheless, its effects on increasing IL-10 were greater than those increasing IFN- γ , showing that lithium has mostly inhibitory immunoregulatory effects. In patients with schizophrenia and mania, lithium and antipsychotics have normalised initially increased levels of acute phase proteins, such as haptoglobin, fibrinogen and hemopexin, and complement factors, e.g. C3C and C4 (Maes et al., 1997b).

A study by Sassi et al (Sassi et al., 2004) used magnetic resonance imaging (MRI) to investigate brain region volumes in healthy volunteers (n=39), untreated bipolar patients (n=11) and lithium treated bipolar patients (n=16), demonstrating that while untreated patients had significantly reduced left anterior and posterior cingulate volumes compared to healthy controls, lithium treated patients did not. A further study of untreated bipolar patients (n=12), lithium treated bipolar patients (n=17) and healthy controls (n=46) found that total grey matter volumes were significantly greater for lithium treated patients than for untreated bipolar patients and for controls (Sassi et al., 2002). These findings are especially pertinent as reduction in anterior cingulate cortex volume is observed with schizophrenia from early illness (Fornito et al., 2008). Lithium (and also valproate) activate the extracellular signal-regulated kinase (ERK) mitogen-activated protein (MAP) kinase pathway, which is a signalling cascade utilised by endogenous growth factors (Gray et al., 2003) and may explain the differences in brain region volumes between treated and untreated bipolar patients.

Both lithium and valproate increase bcl-2 associated athanogene-1 (BAG-1)(Zhou et al., 2005), decreasing cortisol's effects at the glucocorticoid receptor and increasing the chaperoning of vitamin D3 to the nuclear vitamin D receptor. Both these medications, via BAG-1, are therefore likely to exert wider effects on neuronal and immune activations. Lithium induction of BAG-1 prevents chronic unpredictable mild stress from inducing depression(Silva et al., 2008), and the induction of BAG-1 may be relevant to preventing stress induced exacerbations and comorbid depression in schizophrenia. Both lithium and valproate are very effective in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (De Sarno et al., 2008, Lv et al.), highlighting their wider immunoregulatory and neuroprotective efficacy. Lithium has also been shown to enable the use of clozapine when neutropenia is evident(Hodgson and Mendis, 2010).Lastly, lithium has potentially neuroprotective effects on hippocampal microstructure in individuals at ultra-high risk for developing psychosis (Berger et al., 2012).

4.2 Atypical antipsychotics

In addition to reducing symptoms of illness, antipsychotic medication also appear to impede illness progression (Wyatt, 1991). Atypical antipsychotics have been demonstrated in rats to increase newly divided cells in the subventricular zone by 2- to 3-fold (Wakade et al., 2002). Clozapine and olanzapine upregulated, whereas haloperidol downregulated, BDNF in rat hippocampus (Bai et al., 2003). There may be some differences and commonalities in neuroprotective properties between agents. Chen and Huang (Chen and Huang, 2011) measured BDNF in patients treated with risperidone (n=32) or clozapine (n=21), and found that risperidone but not clozapine was associated with raised serum BDNF levels, with the effect strongest in men. The TRYCAT pathway is thought to be an important mediator of

the immuno-inflammatory effects on neuronal activity. Atypical antipsychotics significantly inhibit the neurotoxic TRYCAT products, 3-OHK and QUIN (Myint et al., 2011, Condray et al., 2011), contributing to neuroprotection. However, recent reports have raised concerns that some antipsychotics may be associated with reduction in grey matter; this is an issue of considerable concern, and an active research focus (Moncrieff and Leo, 2010).

4.2.1 Clozapine

In studies of primary neuron-glia cultures, clozapine was shown to be protective against lipopolysaccharide induced neurodegeneration, with further studies suggesting that clozapine has a neuroprotective effect by reducing microglial activation through limiting production of reactive oxygen species (Hu et al., 2012). Serum BDNF was upregulated by clozapine in a dose dependant response in two studies of patients with schizophrenia (n=31) (Pedrini et al., 2011, Grillo et al., 2007).

Treatment with clozapine concentration-dependently increases the levels of sIL-2R in schizophrenic patients (Maes et al., 1994). Since increased levels of sIL-2R in the serum may bind IL-2 and thus prevent the activities of this cytokine, increased sIL-2R levels has immunosuppressive effects (Maes et al., 1994). In addition, clozapine also increases the levels of CC16 (Clara cell protein or uteroglobulin) and soluble interleukin -1 receptor antagonist (sIL-1RA) in schizophrenic patients (Maes et al., 1997a). CC16 is an endogenous anti-inflammatory compound that exhibits strong anti-inflammatory properties. Patients with schizophrenia have significantly lowered plasma levels of CC16. Clozapine also increases the plasma levels of sIL-1RA, which inhibits IL-1 signalling (Maes et al., 1997a, Song et al., 2000). Clozapine and other antipsychotic agents may additionally increase the anti-inflammatory capacity

by increasing plasma levels of the leukaemia inhibitory factor receptor (LIF-R)(Maes et al., 2002).

4.2.2 Aripiprazole

In vitro studies have demonstrated that aripiprazole modulates pathways that may be neuroprotective. Koprivica et al (Koprivica et al., 2011) found that aripiprazole, but not risperidone or olanzapine, inhibited glutamate induced neurotoxicity in cultured rat neurons. Park et al (Park et al., 2009) found that aripiprazole, but not haloperidol, raised levels of BDNF, ~~Glycogen synthase kinase-3 beta~~ GSK-3 β phosphorylation and Bcl-2 in a human neuroblast cell culture. Elsewhere, Park et al (Park et al., 2011) found that aripiprazole and olanzapine, but not haloperidol, were protective against reduced BDNF, GSK-3 β and β -catenin in rat hippocampus with immobilisation stress and increased the levels of BDNF, GSK-3 β and β -catenin when immobilisation stress was not administered.

4.2.3 Olanzapine

As with aripiprazole, olanzapine increases BDNF, GSK-3 β and β -catenin in vitro (Park et al., 2011). Lu et al (Lu et al., 2004b) found that olanzapine activates cell signalling pathways associated with neurotrophic factors and also compared favourably to other antipsychotics in a series of in vitro experiments demonstrating that olanzapine, but not clozapine, had a mitogenic effect on a neuronal cell culture and was protective against neuronal cell death in nutrient deprived cultures, whereas fluphenazine and risperidone were associated with greater cell death in the same cell culture conditions. Yulug et al (Yulug et al., 2008) showed that olanzapine was associated with a smaller penumbra in a mouse model of cerebral ischemia,

however this was only found for a low dose (0.1 mg/kg) and the effect was lost at a higher dose.

4.2.4 Paliperidone

Yang and Lung (Yang and Lung, 2011) demonstrated that paliperidone has greater antioxidant properties than other atypical antipsychotics and was superior to haloperidol, olanzapine and risperidone for protecting a neuronal cell line against hydrogen peroxide induced cell death.

4.2.5 Quetiapine, ziprasidone, lurasidone and perospirone

Bian et al (Bian et al., 2008) investigated the anti-inflammatory effects of quetiapine, ziprasidone and perospirone on interferon- γ activated microglial cell lines and found that all three atypical antipsychotics significantly inhibited nitric oxide release, however quetiapine and perospirone but not ziprasidone inhibited TNF- α . Lauterbach et al (Lauterbach et al., 2010) report that ziprasidone inhibits GSK-3 β , may inhibit synthesis of nitric oxide (NO) and other free radicals, mitochondrial depolarization, apoptosis, microglial activation and may upregulate BDNF and GDNF. Lurasidone increases BDNF mRNA and BDNF protein expression in rat prefrontal cortex (Fumagalli et al., 2012).

5. Antidepressants

Meta-analyses have suggested that antidepressants may normalise cortical volumetric abnormalities associated with major depression (Bora et al., 2011d). Hashioka et al (Hashioka et al., 2007) reported that fluvoxamine, reboxetine and imipramine reduce microglial activation and inhibit production of the pro-inflammatory cytokine IL-6 and NO. Lauterbach et al (Lauterbach et al., 2010) reported inhibition

of production of NO, GSK-3 β and upregulation of BDNF and Glial cell line-derived neurotrophic factor (GDNF) as overlapping properties of antidepressants. In addition, duloxetine and nortriptyline inhibit mitochondrial permeability, and imipramine inhibits TNF- α (Lauterbach et al., 2010). Sertraline was shown to increase BDNF and promote neurogenesis in a murine model of Huntington's disease (Peng et al., 2008b). Paroxetine was shown to suppress expression of astroglial myeloperoxidase and/or production of NADPH oxidase-derived reactive oxygen species and to reduce expression of proinflammatory cytokines, IL-1 β , TNF- α , and inducible NO synthase in a murine model of Parkinson's disease (Chung et al., 2010). Fluvoxamine was suggested to have neuroprotective properties through sigma-1 receptor agonism (Hashimoto, 2009). Fluoxetine was suggested to have neuroprotective anti-inflammatory effects through inhibition of NFkappaB (Lim et al., 2009), IL-1 β , TNF- α , and COX-2 (Jin et al., 2009). Desipramine and venlafaxine modulate the apoptosis regulator protein Bcl-2 expression and desipramine inhibits lipopolysaccharide induced neuronal stem cell apoptosis in vitro (Huang et al., 2007). Imipramine was demonstrated to modulate BDNF, Mitogen activated protein kinase, ERK pathway and Bcl-2 and inhibit lipopolysaccharide induced neuronal stem cell apoptosis in vitro (Peng et al., 2008a). Paroxetine, sertraline and clomipramine showed immunomodulatory activity in concanavalin A activated rat splenocyte, inhibiting TNF- α , COX-2 and Bcl-2 (Taler et al., 2008) and paroxetine and sertraline were also shown to be immunomodulatory in human T-cells (Taler et al., 2007).

It is understood that the antidepressant activity of different antidepressant drugs may be explained by their activities at different pathways. In this regard:

- 1) antidepressants significantly suppress M1 macrophage production of pro-inflammatory cytokines;

- 2) antidepressants suppress the production of Th1-like cytokine such as IFN- γ and increase that of IL-10;
- 3) antidepressants exert anti-O&NS effects and increase the antioxidative potential;
- 4) antidepressants protect mitochondria from the damaging effects of O&NS;
- 5) antidepressants have neuroprotective effects (Maes et al., 2012).

A recent review showed that antidepressants decrease apoptotic pathways by suppression of the production of caspase-3 and increasing that of Bcl-2 and Bcl-xl (Kubera et al., 2011). In addition, antidepressants increase the expression of different neurotrophic factors including the tyrosine-related kinase B receptor for BDNF (Kubera et al., 2011).

6. Other pharmaceutical agents

6.1 *Minocycline*

Minocycline is a tetracycline antibiotic that crosses the blood brain barrier. It has been demonstrated to have anti-oxidative, anti-inflammatory and anti-apoptotic properties, and has been put forward as a potential therapeutic and neuroprotective agent (Dean et al., 2012). Minocycline has been shown to reduce oxidative stress in pre-clinical models by reducing lipid peroxidation (Ahuja et al., 2008) and peroxynitrite-induced DNA damage (Schildknecht et al., 2010). Furthermore, it has been shown to improve oxidative defences including increasing superoxide dismutase levels following NMDA treatment (Garcia-Martinez et al., 2010). Interacting with inflammatory mediators, minocycline has been shown to reduce

nitrite and nitric oxide synthase levels following lipopolysaccharide treatment (Kim et al., 2004). Minocycline directly impacts on inflammatory cytokines with preclinical studies showing reductions in TNF- α (Pabreja et al., 2011), IL-1 β (Homsy et al., 2009, Orio et al., 2010), PGE₂ (Kim et al., 2004) and COX-2 (Kim et al., 2004) in models of induced inflammation. In addition to preventing cellular damage by attenuating inflammation and oxidative stress, minocycline assists in neurogenesis and the prevention of apoptosis. Survivin and Bcl-2 were restored following minocycline treatment and subsequent reductions in apoptosis were noted (Garner et al., 2003, Kernt et al., 2010). Neuroprotective effects have also been shown in pre-clinical models where overexpression of BDNF were attenuated (Zhang et al., 2012). Additionally, minocycline prevented hydrogen peroxide-induced blockade of insulin growth factor-1 in murine cortical neurons deprived of neurotrophic factors (B27) (Zhong and Lee, 2007).

There have been several reports of serendipitous improvements in psychiatric domains following microbial treatment with adjunctive minocycline that have indicated its potential as a psychiatric treatment (Chaves et al., 2010, Levine et al., 1996, Miyaoka et al., 2007, Tanibuchi et al., 2009). These reports led to several small adjunctive studies to explore the potential of minocycline as a treatment in psychiatry. In a study of schizophrenia, open-label minocycline treatment (300 mg/day) over four weeks lead to significant reductions in symptoms based on the Positive and Negative Symptoms Scale (PANSS) and these benefits persisted at the four-week follow-up visit (Miyaoka et al., 2008). A small open-label study investigating obsessive compulsive disorder found 200 mg/day of minocycline (in addition to SSRI treatment) had no impact on the symptoms experienced by participants (Rodriguez et al., 2010).

Double-blind randomised controlled trials (RCT) are considered the gold-standard in clinical research and will provide more definitive results regarding minocycline's potential in psychiatry. A RCT in schizophrenia has recently been conducted where 200 mg/day of minocycline was compared to placebo (in addition to antipsychotic treatment) over 22 weeks of treatment. Results showed improvements on negative symptoms, global clinical impression, functioning and cognition following minocycline treatment, although specific improvements on the PANSS were not noted (Levkovitz et al., 2010). A short (4 days) RCT of 200 mg/day minocycline was conducted in 12 smokers. Results showed no effects on number of cigarettes smoked or biochemical measurements of nicotine use. However, there were trends towards decreased cravings and amelioration of depressed mood in those treated with minocycline (Sofuoglu et al., 2009). Finally, a six-week RCT of 150 mg/day of minocycline (in addition to stable antidepressant treatment) was conducted in participants diagnosed with psychotic depression. Results showed improvements in both depressive (Hamilton Depression Rating Scale) and psychotic (Brief Psychiatric Rating Scale) symptoms following minocycline treatment (Miyaoaka et al., 2012). To date, the RCTs that have been conducted exploring minocycline's potential in psychiatry have been limited by small sample sizes and/or short durations of treatment. The author's themselves agree that larger studies are required to make more definitive statements.

6.2 Statins

Statins (hydroxymethylglutamyl coenzyme A (HMG CoA) reductase inhibitors) are cholesterol lowering agents that also modulate inflammatory responses (Rosenson and Tangney, 1998). Lovastatin, mevastatin, pravastatin, simvastatin, cerivastatin, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin were investigated as potential

neuroprotective agents by assessing (i) potential blood-brain barrier penetration, (ii) hypocholesterolemic activity in neurons, (iii) direct neuroprotection, and (iv) biosafety of the treatments, identifying important differences between agents and suggesting superiority for simvastatin (Sierra et al., 2011). However, in a study by Sironi et al. (Sironi et al., 2005) rosuvastatin, but not simvastatin, attenuated the transcription of monocyte chemoattractant protein-1, transforming growth factor-beta1, IL-1 β , and TNF- α in the kidney, and of P-selectin in brain vessels and increased the transcription of endothelial nitric oxide synthase mRNA in the aorta. Gamma-interferon induction of major histocompatibility complex (MHC) class II expression in human endothelial cells was reduced by simvastatin, consequently inhibiting MHC-II-mediated T-cell activation (Kwak et al., 2001). Rosuvastatin reduced markers of oxidative stress and inflammatory markers in spontaneously hypertensive rats, lessened pro-inflammatory cytokines and endogenous nitric oxide synthase inhibitor levels, increased IL-4 and reduced reactive oxygen species production in circulating monocytes (Sicard et al., 2008). Rosuvastatin reduced inflammation and oxidative stress serum markers IL-6 and TNF α in an open parallel-group study of 48 patients with hypertension and dyslipidemia (Gomez-Garcia et al., 2007). Link et al. (Link et al., 2006) gave rosuvastatin (20 mg/day) or placebo to patients with troponin positive acute coronary syndrome and found a reduction of TNF- α and IFN- γ production in stimulated T-lymphocytes, and inhibited Th-1-immune response within 72 hours of rosuvastatin treatment. Mayer et al. (Mayer et al., 2007), incubated human hepatoma cells and primary human hepatocytes with rosuvastatin (0.3 - 1 microM) for 24 hours and found reduces IL-6 induced expression of C - reactive protein, suggesting a hepatic source of its anti-inflammatory effects. Kim et al. (Kim et al., 2007)

incubated TNF- α stimulated human endothelial cells with rosuvastatin, which inhibited c-Jun N-terminal kinase and nuclear factor kappa B.

Studies in human promyelocytic cells (HL-60) showed rosuvastatin upregulated glutathione synthesis and inhibited DNA damage induced by phorbol 12-myristate 13-acetate (PMA) or by hydrogen peroxide. Rosuvastatin prevented PMA-provoked formation of reactive oxygen species. Pre-incubation of cells with rosuvastatin resulted in a protective effect even after its removal from the incubation medium. Increased total glutathione may be mediated via upregulation of gamma-glutamylcysteine synthetase (Schupp et al., 2008). In a transgenic rat study rosuvastatin significantly decreased accentuated myocardial NADPH oxidase subunits gp91(phox), p40(phox), p22(phox), and Ras-related C3 botulinum toxin substrate (RAC1) expression, and these changes were accompanied by a parallel reduction in myocardial lipid peroxidation (nitrotyrosine and malondialdehyde content) (Habibi et al., 2007). Rosuvastatin is able to protect against lipid peroxidation and free radical DNA damage because of its reducing equivalent donating property or direct hydroxyl radical-scavenging activity (Ajith et al., 2008). Deficits in the provision of statin medication to people with schizophrenia have been suggested to contribute to the high levels of deaths from cardiovascular disorders (Mitchell and Lord, 2010).

6.3 Aspirin

Aspirin (acetylsalicylic acid) is a commonly used anti-inflammatory agent that acts to impair inflammatory cascades through inhibiting cyclo-oxygenase pathways, and suppressing production of thromboxanes and prostaglandins (Vane and Botting, 2003). In addition, it is now clear that aspirin may exert effects on other modulators

of inflammation and O&NS. Aspirin was shown trigger the synthesis of 15-epi-lipoxin A₄, which increases plasma nitric oxide by inhibiting leukocyte-endothelium interactions and resulting in anti-inflammatory effects (Paul-Clark et al., 2004). In a treatment intervention of 70 patients with depression, giving aspirin together with fluoxetine conferred a greater reduction of oxidative stress parameters than fluoxetine monotherapy (Galecki et al., 2009). Aspirin combined with sulfasalazine had neuroprotective effects in two rodent models of ischemia (Gwag et al., 2007). Aspirin moderated the inflammatory response in lipopolysaccharide activated microglia by triggering lipoxins, inhibiting activation of NO, IL-1 β , TNF- α , NF kappaB, ERK and MAP kinase (Wang et al., 2011). Aspirin does not cross the blood brain barrier, suggesting that efficacy in mental health treatment is likely to be a downstream effect. Interestingly recent data suggests that some of the effects of the aspirin metabolite are mediated via the activation of the G-protein coupled receptor-35 (GPR35), which is known to be antinociceptive and to modulate immune cell responses (Deng and Fang, 2012). This would suggest that some of the benefits of aspirin are exerted outside of cyclooxygenase inhibition and are mediated via the activation of the GPR35, which may be of particular relevance to the high levels of somatization that are often comorbid with schizophrenia and mood disorders (Lipowski, 1990, Ritsner, 2003). These effects may interact with the tryptophan catabolite (TRYCAT) pathway, given that kynurenic acid (KYNA) is also a GPR35 agonist (Moroni et al., 2012), with decreased KYNA being evident in somatization (Maes and Rief, 2012).

7. Nutritional and other agents

7.1 *Mitochondrial enhancers*

A study of 36 adults with mitochondrial cytopathies found high rates of bipolar disorder, depression and panic disorder (Fattal et al., 2007). Abnormalities in energy generation have been observed for bipolar disorder and schizophrenia (Clay et al., 2011). Mitochondria are particularly active in oxygen rich, highly energy dependent tissues, such as the brain. Impaired energy metabolism triggers pro-apoptotic signalling (programmed cell death), oxidative damage and excitotoxicity, as well as impeding mitochondrial DNA repair. Haloperidol and fluphenazine inhibit mitochondrial complex I activity and may adversely affect mitochondrial function (Prince et al., 1997). Lithium and antidepressants such as paroxetine increase mitochondrial energy generation (Hroudova and Fisar, 2010, Maurer et al., 2009).

Agents that enhance mitochondrial function may be neuroprotective for people with mental illnesses (Nierenberg et al., 2012), suggested by a link between mitochondrial abnormalities and some mental disorders (Brady et al., 2012). These agents may need to be taken in combination, and with the addition of other co-factors, to exert an effect. These include agents that specifically improve lactic acidosis, antioxidants, agents that correct secondary biochemical deficiencies, respiratory chain co-factors, and hormones (Finsterer, 2010). At least one clinical trial is currently underway (Australian clinical trial registry number ACTRN12612000830897).

7.2 Melatonin

Melatonin levels have been reported as decreased in mood disorders and schizophrenia (Monteleone et al., 1997). As well as entraining the circadian rhythm, melatonin is a powerful anti-inflammatory, anti-oxidant, inducer of endogenous antioxidants, and increases mitochondrial oxidative phosphorylation (Martin et al., 2002). Melatonin is significantly decreased by some antipsychotics, especially olanzapine

(Raskind et al., 2007) and this may contribute to the metabolic dysregulation and weight gain induced by antipsychotics and mood stabilizers (Anderson and Maes, 2012a). One of the effects of valproate is to dramatically increase the levels of melatonin receptors in astrocytes (Castro et al., 2005), suggesting that the adjunctive use of melatonin would significantly modulate the central effects of this mood stabilizer.

7.3 Leptin

The weight gain and wider metabolic dysregulation induced by antipsychotics and mood regulators is relevant to the modulation of the immuno-inflammatory response and significantly contributes to the 25 year decrease in life-expectancy for people with schizophrenia (Flaum, 2010). These metabolic effects are associated with increased levels of leptin and subsequent leptin resistance, with single nucleotide polymorphisms in the leptin gene being linked to weight gain and metabolic dysregulation in schizophrenia (Kuo et al., 2011). This is important to wider immune regulation as leptin, like melatonin, is a significant immune modulator, suggesting that the weight gain and metabolic dysregulation of these medications will be interacting with their effects on immuno-inflammatory responses. Increased peripheral leptin and leptin resistance is associated with a decrease in leptin transport over the blood-brain-barrier (BBB), resulting in decreased leptin feedback in the central nervous system. Some of the inhibitory effects on leptin transport over the BBB are mediated by increased triglycerides (Banks, 2012). In diet induced obese rodents, melatonin decreases levels of triglycerides and leptin resistance (Rios-Lugo et al., 2010). As with other antipsychotics, olanzapine increases levels of circulating triglycerides (Zugno et al., 2012). The efficacy of statins in schizophrenia is associated primarily with decreased triglycerides, suggesting that

this could have longer-term consequences for central leptin activity(Hanssens et al., 2007).

Lower levels of leptin appear to predispose to depression risk(Pasco et al., 2008). Leptin is generally neuroprotective and is generating some interest as a potential anti-depressant, andneuroprotective agent for Alzheimer's disease (Dietrich et al., 2008). Leptin is negatively coupled to the adenylyl cyclase/cAMP pathway and also inhibits the effects of cortisol at the glucocorticoid receptor (GR). As such leptin, via decreased cAMP and cortisol effects, will decrease the induction of tryptophan 2,3-dioxygenase (TDO) in astrocytes, inhibiting kynurenine and KYNA production, leading to increased activation of the alpha-7 nicotinic acetylcholine receptor and subsequently increasing and optimising levels of cortical arousal, with subsequent benefits on cognition(Zmarowski et al., 2009). It remains to be tested as to whether leptin increases levels of BAG-1, as its induction of bcl-2 and GR inhibition could suggest. If leptin does increase BAG-1, it would be likely to significantly modulate stress, immunogenic and apoptotic effects of cortisol. Leptin, if targeted to the CNS, could be an important modulator of the changes associated with schizophrenia and mood disorders. Some data shows that leptin also regulates the levels of melatonin and N-acetylserotonin (NAS) production, via the induction of arylalkylamine-N - acetyltransferase gene (AANAT) in the pineal gland(Gupta et al., 2010). NAS activates the BDNF trkB receptor(Jang et al., 2010), suggesting overlaps with other neuroprotective psychotropic medication. Given the antipsychotic induced peripheral leptin resistance and the lack of BBB around the pineal gland, it remains to be determined as to whether leptin resistance contributes to the decrease in levels of pineal melatonin production in schizophrenia and mood disorders.

7.4 Omega-3 Polyunsaturated Fatty acids

Linolenic acid and docosahexaenoic acid may be neuroprotective against ischaemic and neurotoxic (kainate) insults in rodents by modulating two-pore K^+ channels receptors TREK-1 and TRAAK (Lauritzen et al., 2000). TREK-1 and TRAAK are implicated in sensitisation to pain from mechanical stimulation and temperature (Noel et al., 2009). Studies in rodents have also demonstrated that eicosapentaenoic acid and docosahexaenoic acid inhibit an inflammatory response in microglia, reducing IL-6, IL-1 α , IL-1 β and TNF- α response after ischaemic and lipopolysaccharide insult (Zhang et al., 2010). Omega-3 polyunsaturated fatty acids (PUFAs) have generally shown some efficacy in mood disorders, especially depression in bipolar disorder (Sarris et al., 2012), with a recent systematic review suggesting the need for further research in wider psychiatric disorders (Politi et al., 2012). This includes research into effects in schizophrenia, where despite a recent meta-analysis of the omega-3 PUFA, eicosapentaenoic acid, finding no short-term benefit in established schizophrenia, recent research suggests possible effects of omega-3 PUFA's in preventing conversion of ultra-high risk individuals to threshold psychosis. This may be indicative of a neuroprotective effect, possibly mediated by changes in nervonic acid (Amminger et al., 2011). Any longer-term or relapse prevention effects however require further investigation (Fusar-Poli and Berger, 2012).

7.5 Erythropoietin

Erythropoietin (EPO) is well tolerated, can cross the BBB and has been shown to reduce haloperidol induced neuronal death in-vitro, whilst enhancing cognitive functioning in mice (Ehrenreich et al., 2004). EPO has been demonstrated to increase BDNF and reduce neuronal death in primary cultures of rat hippocampal neurons treated with the neurotoxin trimethyltin (Viviani et al., 2005). The impacts of EPO centrally on neurogenesis, neuroprotection and inflammation modulation

suggest potential efficacy in the treatment of schizophrenia(Fond et al., 2012). However, caution is warranted as EPO may increase the risk of thrombosis and cancer, as well as increased metabolic rate and mean arterial blood pressure, potentially leading to cerebral ischemia(Fond et al., 2012). It remains to be determined as to whether the adjunctive use of melatonin, which would be expected to inhibit these side effects, would make EPO more tolerable over the longer-term. A combination of EPO and melatonin in treatment of dinitrobenzene sulfonic acid-induced colitis has proved more efficacious in other medical conditions, than either used alone(Tasdemir et al., 2011). Proof of concept studies suggest potential antidepressant effects as well(Miskowiak et al., 2012).

7.6 N-acetylcysteine

N-acetyl cysteine (NAC) targets a number of molecular pathways including neurotrophins, glutamatergic transmission, glutathione, apoptosis, mitochondrial function and inflammatory pathways. These pathways are germane to a range of neuropsychiatric disorders. Cysteine plays a role in regulating intra- and extracellular exchange of glutamate via cysteine glutamate exchange, also called the cystine-glutamate antiporter(Baker et al., 2002).Glutathione potentiates the NMDA response to glutamate. NAC modulates dopamine transmission and blocks the dopamine induced formation of reactive oxygen species(Kaushal et al., 2012).By boosting cysteine, the rate limiting step for glutathione production, NAC increases glutathione available for redox defences(Dean et al., 2011b). NAC enhances neuronal differentiation from embryonic stem cells and promotes neuronal sprouting and regeneration(Qian and Yang, 2009).NAC reverses models of mitochondrial toxicity and normalises mitochondria-associated factors including lactate levels and pyruvate(Lee et al., 2012). Lastly NAC has anti-inflammatory properties, linked to

oxidative pathways, which may provide another potential neuroprotective pathway(Ferreira et al., 2012).

There are positive trials of NAC in neuropsychiatric disorders including autism, cocaine, cannabis abuse, cigarette smoking, compulsive and grooming disorders, schizophrenia, depression and bipolar disorder(Berk et al., 2012, Dean et al., 2011a, Berk et al., 2011a, Dodd et al., 2008). Its neuroprotective potential is suggested by pilot trials in dementia. Its benign tolerability profile, its action on multiple operative pathways and the emergence of positive trials make it a viable neuroprotective target.

7.7 Haematopoietic neuroprotective cytokines

Stem cell factor (SCF) and granulocyte-colony stimulatingfactor (G-CSF) are hematopoietic growth factors that have demonstrated neuroprotective effects in rodent models of brain injury (Zhao et al., 2007c, Charles et al., 2012, Khatibi et al., 2011, Fathali et al., 2010). SCF was shown to be neuroprotective against camptothecin-induced apoptosis and glutamate excitotoxicity in rat cortical neurons, mediated by Akt and ERK, as well as NFkappaB-mediated gene transcription (Dhandapani et al., 2005). SCF and G-CSF are able to pass through the blood-brain barrier (Zhao et al., 2007b). These agents have been demonstrated to improve functional outcomes and restore neurological deficits (Zhao et al., 2007a, Wang et al., 2012), suggesting that they may be worth evaluating in schizophrenia and other disorders marked by a neuroprogressive course.

Discussion

Insights into the neuropathological mechanisms underpinning the aetiology of many psychiatric disorders suggest a number of readily available and experimental agents may be capable of exerting neuroprotective effects. Many potential neuroprotective agents are currently available, however more evidence about the clinical benefits of neuroprotection in mental health is required if neuroprotective strategies are to become part of routine care in mental health. The potential benefits of neuroprotection are manifold. There would be considerable clinical value in agents that may prevent cognitive decline and impede illness progression, however conclusive evidence that putative neuroprotective agents have efficacy for these outcomes remains elusive.

Currently, evidence supports a role for these agents in modulating apoptotic, neurotrophic, inflammatory, and oxidative processes as well as for the prevention of morphological brain changes. Intuitively these effects should be beneficial, however there is a paucity of prospective, maintenance treatment studies to assess the efficacy of these agents on mental health outcomes. Many of the putative neuroprotective agents do not yet have an evidence base for treatment efficacy, and those agents that are useful in acute illness are known to have mechanisms of action other than neuroprotection.

In addition, agents such as modafinil (Antonelli et al., 1998) have neuroprotective properties and are effective for neurodegenerative disease such as Alzheimer's and Parkinson's diseases, but have not been shown to benefit those with primary mental disorders. Indeed, the differences and similarities between neuroprotective agents for neurology and psychiatry are not well defined. Although agents that protect against plaques and neurofibrillary tangles are of benefit for the treatment of dementias, it is unclear which, if any, of these neuroprotective mechanisms of action

may be associated with clinically measurable benefit in mental illness. To some extent this may be linked to the heterogeneity of both psychiatric and degenerative disorders, placing a research burden on more clearly defining the biological underpinnings in both etiology and course. More refined treatment targets at different stages may then follow.

Some agents protect against neurodegeneration (antioxidants and antiapoptotic agents) whereas other agents promote growth factors. The benefits of modulating neurotrophic and apoptotic factors are not well understood, especially as these factors are well regulated by complex pathways. For example, GSK-3 β is upregulated by some putatively neuroprotective agents and inhibited by others, with unclear effects. Neuroprotective clinical strategies may require treatment with more than one agent. Individual agents may need to be combined with other therapies to exert clinically meaningful effects. Alternatively, individual agents may only be neuroprotective against specific toxins or insults. Investigations of ischemia in rodents have shown that imipramine is a more effective neuroprotective agent when combined with PEP-1-catalase (Kim et al., 2011) and that lithium is a more effective neuroprotective agent when combined with prostaglandin E1 (Sheng et al., 2011). An understanding of the fine grained, dynamic inflammatory/anti-inflammatory and oxidant/anti-oxidant interactions in vivo is far from established, meaning that clinicians and researchers are still painting with a wide brush in their conceptualisations and treatment of these disorders.

There are many other neuroprotective candidates, especially amongst natural products, most of which have limited data. Further studies are required to establish the neuroprotective properties of psychotropic drugs and natural products, as well as

large clinical trials to evaluate their clinical usefulness, making this a vibrant, and potentially fruitful arena for future research.

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	MRI evidence of prevention of brain volumetric changes	Neuroprotective in cell cultures or animal models	Anti-inflammatory action	Anti-oxidant action	Changes to apoptotic, Neurotrophic and other regulatory factors
Lithium	Yes	H ₂ O ₂ treated cortex cells	↓IL-1 β and IL-6 Increase IL-10 and IL-1RA and lower the IFN γ /IL-10 ratio	↑GSH	Bcl-2 BDNF, ERK, MAP kinase
Clozapine		LPS treated neuron-glia cells	Increase IL-1RA, IL-2R, CC16 and LIF-R		BDNF
Aripirazole		Glutamate treated			Bcl-2, BDNF, GSK-

		neurons			3 β , β -catenin
Olanzapine		1. Nutrient deprived cells. 2. Mouse cerebral ischemia.			BDNF, GSK-3 β , β -catenin
Paliperidone		H ₂ O ₂ treated neurons		yes	
Quetiapine		INF- γ treated microglia	\downarrow TNF- α		
Ziprazadone		INF- γ treated microglia	Yes	yes	GSK-3 β , BDNF, GDNF
Perospirone		INF- γ treated microglia	\downarrow TNF- α		
Antidepressants		LPS treated neuronal stem cells	\downarrow IL-6, TNF- α and NO Decrease IFN γ and IL-2 Increase IL-10		GSK-3 β , GSK-3, BDNF, GDNF, Bcl-2, ERK, MAP kinase
Minocycline		1. Glutamate treated neurons. 2.	\downarrow TNF- α	\downarrow lipid peroxidation, \uparrow catalase,	

		Mouse cerebral ischemia.		↑ubiquinone	
Statins			↓IL-6, CRP, NO, IL-1 β , TNF- α , NF-kappaB	↑GSH, ↑SOD1, ↓lipid peroxidation, ↓DNA damage	
Aspirin		Rodent cerebral ischemia.	↓NO, IL-1 β , TNF- α , NF-kappaB		ERK, MAP kinase
Omega-3 PUFA			Lower IL-1, TNF, IFN γ		neuroprotective
Erythropoietin		Trimethyltin treated neurons			↑ BDNF
Melatonin	Yes	Rodent brain; Human brain	↓NO, IL-1 β , TNF- α , NF	↑GSH, ↑ Nrf-2	↑ BDNF, ↑ Bcl-2,

Leptin		cells. ↓MDD, ↓Alzheimer degen	kappaB ↓Cortisol ↑IL-4, IL-10, IFN- γ , IL-2	↑GSH	↑ pGSK-3 β ↑bcl-2 ↑ERK1,2
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Table 1: Neuroprotective properties of agents that may be used for mental health. ↑ - upregulated, ↓ - downregulated LPS – lipopolysaccharide, INF- γ interferon gamma, NF-kappaB nuclear factor kappa B,

Highlights

- In many individuals major neuropsychiatric disorders are a neuroprogressive illness
- Structural brain changes, cognitive and functional decline and poor treatment response may occur
- Some treatments may have neuroprotective properties

ACCEPTED MANUSCRIPT