Neuroscience and Biobehavioral Reviews 36 (2012) 658–676

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Depression and type 2 diabetes: Inflammatory mechanisms of a psychoneuroendocrine co-morbidity

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ARTICLE INFO

Article history:
Received 31 March 2011
Received in revised form 1 October 2011
Accepted 5 October 2011

Keywords:
Depression
Stress
Diabetes
Obesity
Cytokine
Inflammation
Immunity
Glucocorticoid

ABSTRACT

Unipolar depression and diabetes mellitus each account for a significant proportion of the global burden of disease. Epidemiological literature suggests a bi-directional relationship between these two common disorders, and evidence from the molecular sciences supports a role for inflammation in the pathogenesis and pathophysiology of each disorder individually. Recent advances in understanding the neurobiology of depression have implicated dysfunction of the hypothalamus–pituitary–adrenal axis, neurotrophins, and inflammatory mediators in the development of this disorder. Similarly, dysregulated facets of both the innate and adaptive immune system have been implicated in the onset of insulin resistance and type 2 diabetes. This review draws upon an emerging body of epidemiological and mechanistic evidence to support the hypothesis that shared inflammatory mechanisms may represent a key biological link in this co-morbidity. Given the shared mechanisms of this co-morbidity, these patients may be excellent candidates for novel immune targeted pharmacotherapy.

Contents

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doi:10.1016/j.neubiorev.2011.10.001

1. Introduction

Unipolar depression and diabetes mellitus are two of the greatest challenges faced by modern healthcare systems. Both these diseases represent chronic, debilitating conditions that account for a substantial portion of the global burden of disease. The World Health Organisation (WHO) reports that unipolar depressive disorders account for 4.8% of the world's total burden of disease, and this figure increases to 5.1% and 8.2% in middle and high-income countries respectively. Similarly, the International Diabetes Federation (IDF) suggests around 6.6% of the world's population is currently living with diabetes mellitus, a figure which is expected to rise to 7.8% by 2030 (International Diabetes Federation, 2009). Significantly, projections suggest that by the year 2030 unipolar depressive disorders will become the number one contributor to morbidity worldwide and diabetes mellitus will also move into the top 10 (Mathers and Fat, 2008; pp. 28–37). The co-morbidity of these conditions increases the experience of both psychiatric and diabetic symptoms and complications (Gendelman et al., 2009; Katon et al., 2009; Koopmans et al., 2009; Lin et al., 2009, 2010; Maraldi et al., 2007; Molife, 2010; Musselman et al., 2003; Thaneerat et al., 2010; Winkley, 2008), amplifies spending on diabetes-related medical costs two and a half times, and increases total medical costs fourfold (Egede et al., 2002; Le et al., 2006). Additionally, the poorer glycaemic control associated with this co-morbidity is a key risk factor for cardiovascular disease, arguably the most important cause of mortality in high income nations (Richardson et al., 2008). Therefore from both altruistic and health economic points of view, this co-morbidity presents an important target for research and improvements in prevention and therapeutics.

Despite the significance of this relationship, little attention has been given to the biological pathways of this co-morbidity. The few studies that have included assessment of biomarkers found that adjustment for the markers of inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6) does not attenuate the observed relationships between depression and diabetes (Carnethon et al., 2007; Golden et al., 2008; Maraldi et al., 2007). Although these few studies do not support the notion, many authors continue to speculate that inflammation may be the key biological pathway mediating this relationship. This suggestion is based upon the observation that inflammation has been implicated in the pathogenesis and pathophysiology of both depression and type 2 diabetes mellitus (T2DM) independently.

An emerging body of evidence from both human and animal studies demonstrates a reproducible sickness behaviour syndrome in response to elevations levels of cytokines and inflammatory mediators, the symptoms of which are argued to be analogous to depression (Dantzer et al., 2008). Depression is associated with dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis, neurotrophins, neurotransmitters, and inflammatory mediators. These disturbances may extend their influence peripherally through the establishment of a pro-inflammatory milieu which may have impacts on other body systems.

Similarly, several authors have discussed the existence of a pro-inflammatory state in insulin resistance and T2DM, including activation of several of the same aspects of immunity. This is frequently touted as a key link between T2DM and many conditions including those as significant as obesity and cardiovascular disease (Donath and Shoelson, 2011). Additionally, some evidence is emerging regarding the potential for these mediators to access and influence the brain.

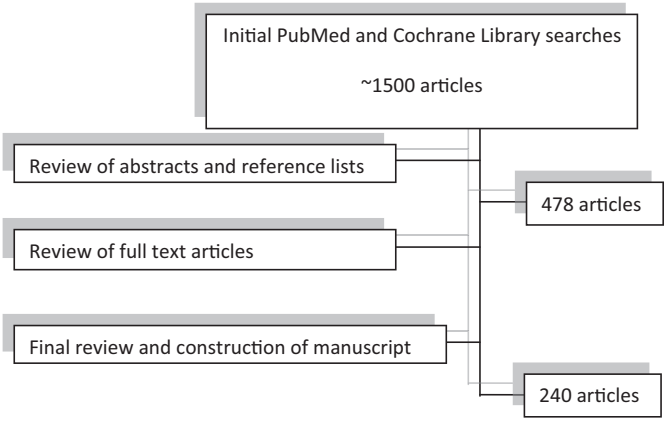

Fig. 1. Study inclusion flowchart.

Although it has previously been proposed that depression and T2DM may share inflammatory mechanisms, no paper has attempted to draw together the existing evidence to support this proposition. This review aims to fill that gap in the literature by undertaking a systematic review of the epidemiological, clinical, and laboratory evidence to support this hypothesis and proposing a mechanistic model of this co-morbidity.

2. Methods

In the construction of this literature review, PubMed and the Cochrane Library were searched with various permutations of the keywords depression, major depressive disorder, diabetes, type 2 diabetes mellitus, insulin resistance, insulin sensitivity, monoamine, neurotransmitter, neuroplasticity, neurogenesis, neurotrophin, glucocorticoid, obesity, adipose, adipokine, metabolic syndrome, cytokine, immune, inflammation, and inflammatory. Articles published online and in English between January 2000 and August 2010 were included. Initial searches yielded a total of approximately 1500 articles. After review of abstracts for relevance to the main aim of this review approximately 500 articles were retrieved and studied. At this stage articles were excluded if their focus was type 1 diabetes, gestational diabetes, or if full text copies could not be retrieved. Articles on type 1 diabetes or gestational diabetes were excluded as the pathogenic processes may not be the same as type 2 diabetes. In addition, articles were obtained from an examination of the reference lists of several reviews on each subtopic. In total 478 articles were retrieved, and the 240 articles with the greatest methodological quality and most significant contribution to the discussion were used in the writing of this review. Fig. 1 depicts this strategy.

We will first discuss the clinical interrelationship between T2DM and depression, then address the mechanistic findings in depression and T2DM. For clarity the evidence implicating inflammatory processes in each of these conditions independently will be described in Section 3. The shared mechanisms and their role as mediators of this bi-directional relationship will then be further discussed in Section 4. Section 3 will also include a brief discussion of the role of obesity as an amplifying factor in this relationship.

3. Clinical association between depression and diabetes

There is a robust epidemiological literature suggesting a degree of co-morbidity between depression and T2DM, however this is primarily made up of cross-sectional studies (Ali et al., 2009; Collins et al., 2009; Disdier-Flores, 2010; Gale et al., 2010; Gendelman et al., 2009; Holt et al., 2009; Kivimaki et al., 2009; Koopmans et al., 2009; Neumiller et al., 2009; Perveen et al., 2010; Thaneerat et al., 2010; Yang et al., 2009). Some studies have found no relationship, however these are by far the minority (Aujla et al., 2009; Fisher et al., 2010). A meta-analysis of early studies determined that there was a statistically significant correlation between depression and T2DM, although the magnitude of this association varied widely between studies, likely due to large variation in definitions and assessment of depression used by each author (Anderson et al., 2001). These cross-sectional studies are useful to establish a correlation between the conditions, however they are not able to determine a temporal relationship or direction of causality.

To determine the temporal relationship of these conditions longitudinal, studies have prospectively examined the relationship between pre-existing T2DM and depression in later life (Aarts et al., 2009; Brown et al., 2006; de Jonge et al., 2006; Engum, 2007; Golden et al., 2008; Katon et al., 2009; Kim et al., 2006; Maraldi et al., 2007; Palinkas et al., 2004; Polsky et al., 2005), and between pre-existing depression (or depressive symptoms) and T2DM in later life (Arroyo et al., 2004; Atlantis et al., 2010; Carnethon et al., 2007, 2003; Eaton et al., 1996; Engum, 2007; Eriksson et al., 2008; Everson-Rose et al., 2004; Golden et al., 2004, 2008; Kawakami et al., 1999; Kumari et al., 2004; Mallon et al., 2005; Stellato et al., 2000; van den Akker et al., 2004). These studies are shown in Table 1. Several subsequent meta-analyses suggest that the relationship between depression and T2DM is bi-directional (Mezuk et al., 2008; O'Connor et al., 2009). The most recent meta-analysis found that the relative risk of T2DM in patients with pre-existing depression is 1.60 (95%CI 1.37–1.88), and the relative risk of depression in patients with pre-existing T2DM is 1.15 (95%CI 1.02–1.30) (Mezuk et al., 2008).

3.1. Mechanistic links

3.1.1. Inflammation and depression

In exploring the mechanisms mediating the bi-directional relationship between depression and T2DM, it is important to look beyond the traditional monoamine model of depression and examine this relationship in the context of other models of depression. Other models that have been proposed would suggest alterations in the function of the hypothalamic-pituitary–adrenal (HPA) axis, the immune system, or neurogenesis play a key role in the pathogenesis of depressive disorders. These models are largely heterogeneous and partly inter-related, and as such a discussion of one must include reference to the others, however the primary focus of this review will be on the inflammatory hypothesis of depression.

The inflammatory hypothesis of depression proposes a bi-directional relationship between inflammation and depression (Maes, 2010; Maes et al., 2009), suggesting that depressive symptoms may be a consequence of activation of various aspects of the immune system both peripherally and centrally, and the neurobiological substrates of depression may contribute to the activation of the immune system. Although the focus of research in this area is primarily on the role of the innate immune system, there is some evidence suggesting that the adaptive immune system may also play a role in an 'immune depression' (Maes, 2010; Miller, 2010). Evidence to support the neuroinflammatory model can be drawn from both human and animal studies. Evidence is provided by the observation that patients with inflammatory conditions including obesity (de Wit et al., 2010), psoriasis (Russo et al., 2004), and rheumatoid arthritis (Dickens et al., 2003) have a higher incidence of depression. Additionally, anti-inflammatory treatment with the TNF-α antagonist etanercept improved symptoms of depression in these patients (Tyring et al., 2006). Cross-sectional studies have found associations between depression and several cytokines and inflammatory mediators. However, the findings of these studies have been largely inconsistent, perhaps due to the heterogeneity in their methods. A recent meta-analysis of cross sectional studies concluded that a statistically significant association with depression exists only for IL-6 and TNF-α (Dowlati et al., 2010). Interestingly, these findings have been contested by an eminent author in the field who argues that strong data was excluded which demonstrates that markers of cell mediated immunity, including T cell activation, Th1 cytokines and their soluble receptors are associated with depression (Maes, 2010). Unfortunately, there remains a paucity of longitudinal studies of this relationship (Table 2). Another source of evidence in humans is the observation that patients treated with interferon therapy often develop psychiatric symptoms similar to those seen in depression (Raison et al., 2005). Similar effects have been observed with IL-2 treatment (Capuron et al., 2002). In addition, these cytokine-induced symptoms respond to traditional antidepressant pharmacotherapy (Raison et al., 2005). These symptoms in humans are analogous to the 'sickness behaviour' syndrome seen in animals when exposed to an infectious agent, a toxin such as lipopolysaccharide (LPS), or direct injection of pro-inflammatory cytokines. The symptoms of 'sickness behaviour' that have been identified include fever, appetite and weight changes, decreased social, voluntary motor, and sexual activity, anhedonia, changes in sleep architecture and cognitive functioning that are all reminiscent of depressive symptoms in humans (Dantzer et al., 2008). Adding to the validity of this model is the finding that these symptoms may be attenuated by treatment with conventional antidepressant medication (Henry et al., 2008). Cytokines also appear to be involved in the response to antidepressant treatment in humans (see for review Janssen et al., 2010). Additionally, a recent study has demonstrated that electroconvulsive therapy has acute effects on the immune function of patients with depression (Fluitman et al., 2010).

Research into inflammation in depression has focussed on the role of cytokines as central mediators of these inflammatory pathways. Many cytokines have been proposed to play a role in the pathogenesis or pathophysiology of depression including TNF-α, INF-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, Il-10, and IL-12. The strength of evidence for the involvement of each varies significantly. In order for elevated levels of these cytokines to access the brain and exert an influence on behaviour they must first cross the blood–brain barrier (BBB). Given the large molecular mass of these cytokines (approximately 15–15 kDa), it is clear that passive diffusion would be an ineffective method of transport. Evidence supports four pathways that cytokines may use to gain access to the central nervous system (CNS) (Quan and Banks, 2007).

3.1.2. Crossing the blood–brain barrier

In the first pathway, cytokines interact with specific receptors on afferent peripheral nerves including the vagus nerve resulting in neuronal transduction of the signal into the CNS where they activate microglia to produce cytokines centrally (Bluthe et al., 1994; Quan and Banks, 2007; Romeo et al., 2001; Watkins et al., 1994). A second pathway involves activation of perivascular macrophage-like cells and endothelium in the circumventricular organs including the organum vasculosum of the lamina terminalis, the subfornical organ, the median eminence, the area postrema, and the choroid plexus (Shelton and Miller, 2010). Cytokines act on receptors in these areas to stimulate transduction of these signals to areas inside the BBB (Quan and Banks, 2007). These areas are highly vascular and lack tight junctions between cells allowing the diffusion of cytokines, however the current opinion is that leakage

Table 1
Longitudinal studies of the bidirectional relationship of depression and diabetes.

Author	Direction of association	Diabetes definition	Depression definition	Risk estimate (95%CI)
Aarts et al. (2009)	Diabetes → depression	FPG ≥ 125 mg/dl	Diagnostic interview using ICPC criteria	1.31 (1.18–1.46)
Brown et al. (2006)	Diabetes → depression	>2 diabetes related registry entries within 2 years and/or hypoglycaemic medication use	Antidepressant use and depression related registry entry within 3 months	1.04 (0.94–1.15)
Golden et al. (2008)	Diabetes → depression	FPG ≥ 126 mg/dl or use of diabetic medication	CES-D score >15 and/or antidepressant use	1.52 (1.09–2.12) for treated patients with diabetes 0.73 (0.41–1.30) for untreated patients with diabetes
de Jonge et al. (2006)	Diabetes → depression	Self-report	GMS-AGECAT score > level 3	1.42 (1.04–1.93)
Kim et al. (2006)	Diabetes → depression	Self-report	GMS-AGECAT score > level 3	1.0 (0.4–2.5)
Maraldi et al. (2007)	Diabetes → depression	Self-report and/or hypoglycaemic medication use and/or FPG ≥ 126 mg/dl	CES-D score >15 and/or antidepressant use	1.31 (1.07–1.61)
Polsky et al. (2005)	Diabetes → depression	Self report	Abbreviated CES-D score > 5	1.11 (0.98–1.41)
Engum (2007)	Diabetes ↔ depression	Self report	HAS-D score > 7	1.24 (0.78–1.98) of diabetes → depression 1.51 (1.27–1.80) for depression → diabetes
Palinkas et al. (2004)	Diabetes ↔ depression	OGTT (>200 mg/dl)	BDI score > 10	0.73 (0.41–1.30) for diabetes → depression 2.50 (1.29–4.87) for depression → diabetes
van den Akker et al. (2004)	Depression → diabetes	ICHPPC-2 code entries	ICHPPC-2 code entries	1.04 (0.84–1.28)
Arroyo et al. (2004)	Depression → diabetes	Self report	MHI-5 score < 52	1.55 (1.27–1.90)
Atlantis et al. (2010)	Depression → diabetes	Self report	PAS score > 5 and/or antidepressant use	2.29 (1.28–4.10) for PAS score 1.80 (0.91–3.57) for antidepressant
Carnethon et al. (2003)	Depression → diabetes	ICD-9 code on death certificate or healthcare facility records or self report	General well-being depression subscale score < 13	2.52 (1.73–3.67)
Carnethon et al. (2007)	Depression → diabetes	FPG ≥ 126 mg/dl L and/or hypoglycaemic medication use	CES-D score > 7	1.63 (1.12–2.36)
Eaton et al. (1996)	Depression → diabetes	Self report	DIS	2.23 (0.90–5.55)
Eriksson et al. (2008)	Depression → diabetes	OGTT (>200 mg/dl after 2 h)	Custom questionnaire[a]	3.3 (1.7–5.7) for men 0.7 (0.3–1.5) for women
Everson-Rose et al. (2004)	Depression → diabetes	Self report and/or FPG ≥ 126 mg/dl	CES-D score > 15	1.66 (1.05–2.61)
Golden et al. (2004)	Depression → diabetes	Self report and/or fasting serum glucose > 125 mg/dl	Vital exhaustion scale	1.63 (1.31–2.02)
Kawakami et al. (1999)	Depression → diabetes	OGTT (>200 mg/dl after 2 h)	SDS score > 47	2.32 (1.03–5.08)
Kumari et al. (2004)	Depression → diabetes	Self report or OGTT (>200 mg/dl after 2 h)	General health questionnaire depression subscale score > 3	1.14 (0.83–1.57)
Mallon et al. (2005)	Depression → diabetes	Self report	Answer to question 'do you feel depressed?'	1.47 (0.48–4.47)
Stellato et al. (2000)	Depression → diabetes	Self report	CES-D score > 15	3.09 (1.34–7.12)

[a]As this is not a standardised questionnaire, it is not clear how relevant to depression this result is ICPC: international classification from primary care; CES-D: the centre for epidemiological studies depression scale; BDI: Beck depression inventory; GMS-AGECAT: geriatric mental state history and aetiology schedule-automated geriatric examination for computer assisted taxonomy; HAS-D: hospital anxiety and depression scale-depression subscale; ICHPPC-2: international classification of health problems in primary care; MHI-5: 5-item mental health index; DIS: diagnostic interview schedule; SDS: Zung self-rating depression scale; FPG: fasting plasma glucose; and OGTT: oral glucose tolerance test.

Table 2
Prospective studies of the relationship between depression and inflammation.

Author/year	Study cohort	Depression definition	Sample	Protein/markers investigated	Significant associations (fully adjusted)
Luukinen et al. (2010)	≥70 YO males and females	SZSRDS ≥ 28 or antidepressant use	Serum	hsCRP	hsCRP (for males only) predicts future depressive symptoms
Forti et al. (2010)	CSBA: ≥65 YO males and females	GDS-30 item ≥ 10 or retrospective diagnosis	Serum and plasma	IL-6, TNF-α, ICAM-1, ACT, CRP	–
Deverts et al. (2010)	CARDIA: 33–45YO males and females	CES-D-20 item ≥ 16	Plasma	CRP	Depressive symptoms predict future CRP increases
Stewart et al. (2009)	PHHP: 50–70 YO males and females	BDI-II	Serum	IL-6, CRP	Depressive symptoms predict future IL-6 increases
Milaneschi et al. (2009)	InCHIANTI: ≥65 YO males and females	CES-D-20 item ≥ 20	Serum and plasma	IL-6, sIL-6R, IL-1β, IL-1ra, IL-18, hsCRP	IL-1ra predicts future depressive symptoms
Maas et al. (2009)	Leiden 85-Plus: ≥85 YO males and females	GDS-12 item ≥ 2	Serum	CRP	CRP predicts future depressive symptoms
Hamer et al. (2009)	ELSA: ≥50 YO males and females	CES-D-8 item ≥ 4	Serum	CRP, fibrinogen	CRP predicts future depressive symptoms
Gimeno et al. (2009)	Whitehall II: 35–55 YO males and females	GHQ-4 item depression subscale (cognitive symptoms only)	Serum	IL-6, CRP	CRP and IL-6 predict future depressive symptoms
van den Biggelaar et al. (2007)	Leiden 85-Plus: ≥85 YO males and females	GDS-12 item	Serum, whole blood	CRP, albumin LPS simulated whole blood release of TNF-α, IL-1β, IL-1ra, IL-6, IL-10	CRP, IL-1β and IL-1ra predict future depressive symptoms
Matthews et al. (2007)	SWAN: 42–52 YO perimenopausal females only	CES-D – 20 item	Plasma	hsCRP, fibrinogen, factor VII, PAI-1, tPA	Depressive symptoms predict future fibrinogen and PAI-1 levels
Boyle et al. (2007)	AFHS: mean age 50.2 YO standard deviation 6.3 years Males only	40-item obvious depression scale from MMPI	Serum	Complement C3 and C4	Depressive symptoms predict future C3 complement activation
Liukkonen et al. (2006)	North Finland 1966 birth cohort. Males and females	HSCL-25 ≥ 1.55 and/or self reported previous diagnosis	Serum	hsCRP	hsCRP predicts future depressive symptoms
Kiecolt-Glaser et al. (2003)	55–89 YO male and female caregivers and controls	BDI-13 item	Plasma	IL-6	–

YO: years old; SZSRDS: Short Zung self rating depression scale; hsCRP: high sensitivity C-reactive protein; CSBA: conselice study of brain ageing; GDS: geriatric depression scale; IL: interleukin; TNF: tumour necrosis factor; ICAM-1; intercellular adhesion molecule-1; ACT: α_1-antichymotripsin; CARDIA: coronary artery risk development in young adults study; PHHP: Pittsburgh healthy heart project; BDI: Beck depression inventory; InCHIANTI: ageing in the Chianti area; CES-D: centre for epidemiological studies-depression scale; sIL-6R: soluble interleukin-6 receptor; IL-1ra: interleukin-1 receptor antagonist; ELSA: English longitudinal study of ageing; LPS: lipopolysaccharide; SWAN: study of women's health across the nation; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator; AFHS: air force health study; MMPI: Minnesota multiphasic personality inventory; and HSCL-25: Hopkins symptom checklist-25 item.

through the circumventricular organs into the CNS is limited by the presence of a tanycytic barrier which prevents free access of these cytokines to other brain regions (Peruzzo et al., 2000). Additionally, there appears to be a role for the interactions of pathogen associated molecular patterns (e.g. LPS) with toll-like receptors on these macrophage-like cells resulting in further inflammatory activation (Quan et al., 1998). Another pathway involves saturable cytokine transporters that allow for a direct transfer of many cytokines across the BBB (Banks et al., 1998; Kastin et al., 1999; McLay et al., 1997; Pan et al., 1997). Many of the transport systems are bi-directional (Quan and Banks, 2007), including the IL-2 transporters which had long been believed to be unidirectional (Lynch and Banks, 2008). The final potential pathway is through the secretions of activated cells of the BBB. When cytokines activate epithelial or ependymal cells of the BBB they may secrete inflammatory mediators into the CNS. These mediators include prostaglandins, nitric oxide, and a variety of cytokines (Inoue et al., 2002).

It is also relevant to note that cytokines produced in the brain may enter the peripheral circulation via the bi-directional transport systems mentioned above, and through re-absorption of CSF (Banks et al., 1989; Gutierrez et al., 1993).

Once the cytokine signal has crossed the BBB it interacts with several brain mechanisms to induce depressive behaviours. These mechanisms have each been linked to depression independently, and the fact that inflammatory signals have the potential to provide a common link between them adds credence to the hypothesis that inflammation may play a key role in the pathogenesis and/or pathophysiology of depression. Fig. 2 depicts these mechanisms.

3.1.3. Monoamines and other neurotransmitters

The dominant model of depression is still the monoamine model which attributes depressive symptoms to alterations in the metabolism or activity of the monoamine neurotransmitters, primarily serotonin (5-HT), noradrenaline (NA), and dopamine (DA) (Schildkraut, 1965). These alterations are also the primary target for current antidepressant medications. It has been proposed that cytokines may interact with the serotonergic neurotransmitter system through two mechanisms – the activation of the enzyme indoleamine 2,3 dioxygenase (IDO), and increasing the rate of 5-HT turnover. Cytokines can activate IDO through several intracellular signalling pathways (including nuclear factor-κB (NF-κB) and p38 mitogen-activated protein kinase pathways (MAPK)) resulting in the breakdown of tryptophan to kynurenine (Fujigaki et al., 2006). This induces tryptophan depletion, and as tryptophan availability is the rate limiting factor in 5-HT synthesis this may contribute to a decreased rate of 5-HT synthesis which has been shown to induce depression-like symptoms in patients with a personal or family history of depression (Ruhe et al., 2007). A second mechanism proposes that cytokines stimulate increases in monoamine uptake and turnover through both increasing the activity and surface density of 5-HT (Zhu et al., 2006), DA (Nakajima et al., 2004), and NA transporters (Moron et al., 2003). Cytokines have also been shown to inhibit DA synthesis through stimulation of nitric oxide (NO) production resulting in a depletion of tetrahydrobiopterin (BH_4), an important co-factor in the rate-limiting step of DA synthesis (Kitagami et al., 2003). Glutamatergic neurotransmission is also affected by inflammation (McNally et al., 2008), and implicated in the pathogenesis of depression (Hashimoto, 2009). The kynurenine produced by IDO is metabolised to kynurenic acid or quinolinic acid, which function as glutamatergic N-methyl-D-aspartate (NMDA) antagonists and agonists respectively. Quinolinic acid is exclusively produced in microglial cells, therefore the activation of microglial cells by inflammatory signal cascades may skew the balance of kynurenic and quinolinic acids towards the latter (McNally et al., 2008; Myint et al., 2007). In addition to direct agonism of NMDA receptors, quinolinic acid leads to an increase in glutamate release (Fedele and Foster, 1993; Luccini et al., 2007; Tavares et al., 2008). The final potential effect cytokines may have on glutamatergic neurotransmission is a reduction in astrocytic glutamate transporters which are responsible for uptake of excess glutamate and prevention of neuronal excitotoxicity (Fuller et al., 2009). Collectively, these disturbances of glutamatergic neurotransmission have the potential to contribute significantly to neuronal excitotoxicity.

3.1.4. Neuroplasticity

A related pathway for inflammatory induction of depression is through effects on neurogenesis and neuroplasticity. Both human depression and animal models of depression have been shown to exhibit a reduced volume in areas of functional relevance to depression, including the hippocampus (Eker and Gonul, 2010; Tata and Anderson, 2010). This could reflect alterations in neurogenesis and neuroplasticity, while these in turn could potentially be influenced by inflammation through several mechanisms. The first is glutamate-mediated excitotoxicity leading to loss of neurons and glial cells (Hamidi et al., 2004; Thornton et al., 2006). Cytokines directly stimulate glutamate release from astrocytes (Thornton et al., 2006), and stimulate the induction of quinolinic acid (see above) resulting in further glutamate release and direct NMDA agonism. Excessive activation of extrasynaptic NMDA receptors results in rapid Ca^{2+} influx, which accumulates in mitochondria providing stimulus for apoptotic cascades including caspase activation and increased generation of reactive oxygen species (ROS) (Hardingham et al., 2002; Maes et al., 2010; Matute et al., 2006). Quinolinic acid also directly contributes to an increase in oxidative and nitrosative stress, aggravating this process (Maes et al., 2010; Santamaria et al., 2001). In conjunction with these mechanisms, depression is associated with a decrease in levels of antioxidants and antioxidant enzymes. The imbalance between oxidative or nitrosative influences and antioxidants results in peroxidation of membrane lipids, oxidative damage to DNA, and nitrosative damage to proteins (Maes et al., 2010). The result of this accumulated damage is that neurons and glial cells die by apoptosis or necrosis (Wang et al., 2009). It is also believed that changes in proteins or lipids may lead to the formation of highly immunogenic new epitopes, therefore triggering an autoimmune response (Maes et al., 2010).

The second mechanism is a reduction in trophic support for neurogenesis. Of the neurotrophins studied in depression, the greatest attention and consistency in results are found for brain derived neurotrophic factor (BDNF) (Castren et al., 2007). In addition to its aforementioned excitotoxic effects, activation of extrasynaptic NDMA receptors has been shown to inhibit the activity of cAMP response element binding (CREB) protein, and thereby block induction of BDNF gene expression (Hardingham et al., 2002). Similarly, a reduction in 5-HT activity may exert downstream effects on BDNF transcription through a reduced activation of 5-HT receptors which are coupled to CREB (Mattson et al., 2004). Therefore it is possible to conceptualise a positive feedback loop between loss of 5-HT neurons due to loss of trophic support, and loss of serotonergic support for neurotrophin release. Additionally, treatment with LPS has been shown to reduce expression of the BDNF receptor tyrosine kinase-B (TrkB) (Wu et al., 2007).

3.1.5. HPA axis

Cytokine-induced hyperactivity of the HPA axis also has the potential to contribute to depression. This hyperactivity has consistently been shown to be associated with depression in humans (Raison and Miller, 2003). Although glucocorticoids (cortisol in humans or corticosterone in rodents) are recognised as potent anti-inflammatory hormones, some evidence suggests that elevated levels of glucocorticoids may co-exist with high levels of inflammatory cytokines in patients with depression (Edwards et al., 2010;

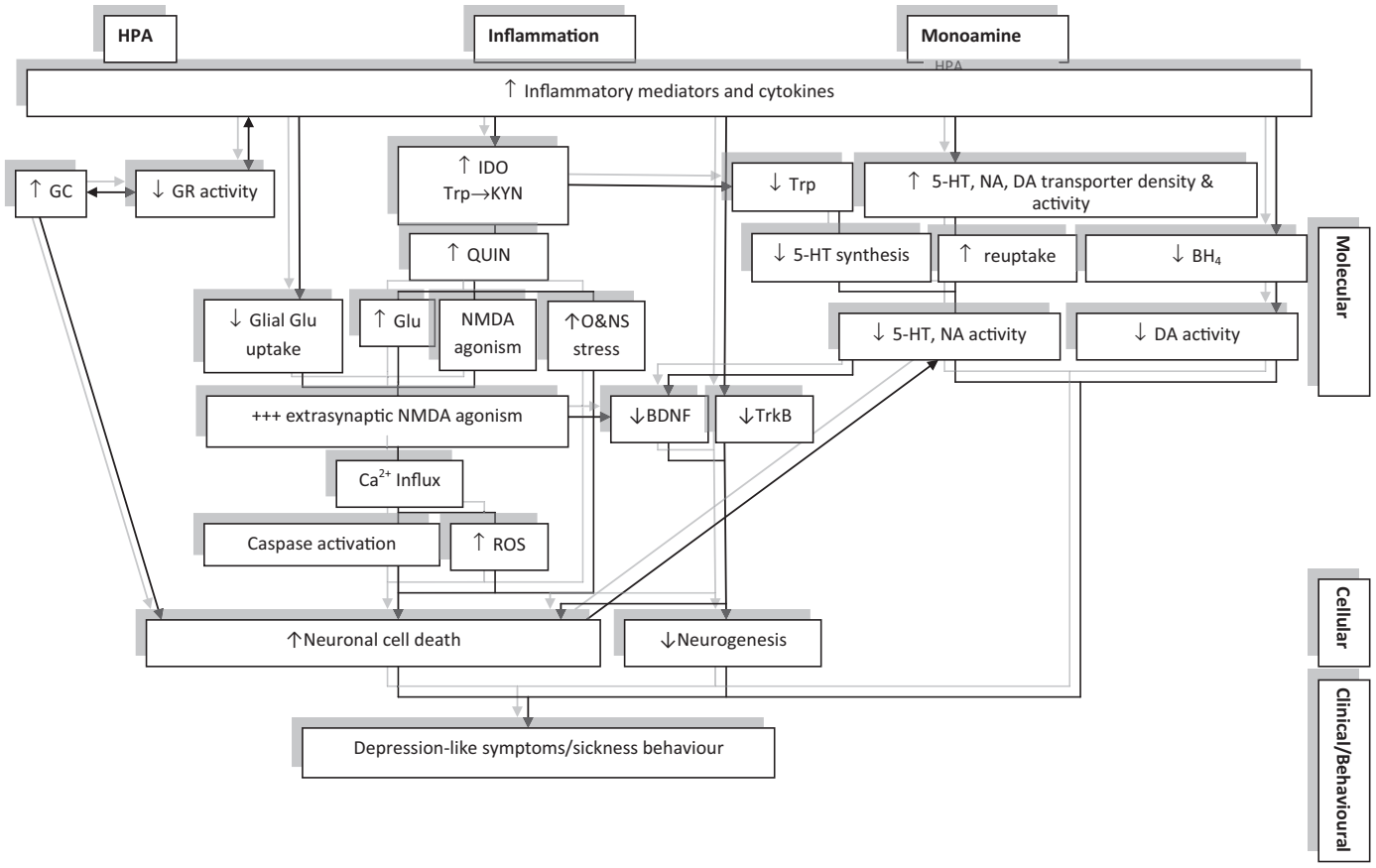

Fig. 2. Inflammation in the pathogenesis and pathophysiology of depression. HPA: hypothalamic-pituitary–adrenal axis; GC: glucocorticoids; GR: glucocorticoid receptor; IDO: indoleamine 2,3 dioxygenase; Trp: tryptophan; KYN: kynurenine; QUIN: quinolinic acid; Glu: glutamate; NMDA: N-methyl-D-aspartate; 5-HT: serotonin; NA: noradrenaline: DA: dopamine; O&NS: oxidative and nitrosative stress; ROS: reactive oxygen species; BDNF: brain-derived neurotrophic factor; TrkB: tyrosine kinase-B; and BH_4: tetrahydrobiopterin.

Jehn et al., 2010; Maes et al., 1993). This is primarily believed to be a reflection of a cytokine-induced disruption of negative feedback via glucocorticoid receptors (GR) at the level of both the hypothalamus and anterior pituitary gland (Pace and Miller, 2009; Raison and Miller, 2003). Evidence for this is drawn from studies that find high rates of non-suppression of HPA hormones in response to administration of dexamethasone (DEX), a potent synthetic glucocorticoid among patients with various depressive disorders (Lopez-Duran et al., 2009). Peripheral immune cells from patients with depression also display reduced sensitivity to glucocorticoids – an effect that is reversed by chronic, but not acute, treatment with conventional antidepressants (Carvalho et al., 2010; Pace et al., 2007; Pace and Miller, 2009). Additionally, polymorphisms in GR genes have been demonstrated in some studies to be associated with depressive disorders (Spijker and van Rossum, 2009). Cytokines have the potential to reduce the activity of GRs at several stages. It has been postulated that cytokines may influence the expression of GRs, although findings in this area have been equivocal (Pace et al., 2007). Some data does however support an effect of cytokines on the relative expression of the α and β isoforms of GR, with a shift towards the inactive β isoform found in patients with depression (Matsubara et al., 2006). Nevertheless, a later study by the same group found no significant difference in patients with major depression (Watanuki et al., 2008). Other potential mechanisms involve disruptions to GR translocation from the cytoplasm to the nucleus and its interactions with DNA and other nuclear proteins including NF-κB (see for review Pace et al., 2007). Further potential effects of cytokines on glucocorticoid homeostasis include activation of 11 beta-hydroxysteroid dehydrogenase – resulting in inactivation of cortisol (Kossintseva et al., 2006), and increasing the activity and expression of the P-glycoprotein pump causing expulsion of glucocorticoids from the cell (Pariante, 2008). Loss of GR negative feedback due to cytokine disruption has the potential to form a pro-inflammatory positive feedback loop where insufficiency of GR activity leads to increased cytokine levels, which then cause further disruption of GR activity (Raison and Miller, 2003). Elevated glucocorticoid levels have also been associated with reduced hippocampal volume (Tata and Anderson, 2010). While some authors have proposed this to be a result of a GR mediated increase in vulnerability to excitotoxicity (Hayley et al., 2005; Raison and Miller, 2003), a recent review suggests that the volume changes associated with glucocorticoid excess likely reflect a loss of synapses and dendritic atrophy rather than a true reduction in cell number (Tata and Anderson, 2010).

3.1.6. Stress and inflammation

The implications of the above mechanisms for the pathogenesis of depression in patients with an infectious, autoimmune, or iatrogenic source of inflammatory stimulation are clear. However, inflammation may also contribute to the development of depression in the absence of a recognised inflammatory condition via the ability of stress to activate the immune system. It has been demonstrated in human and animal literature that both acute and chronic stress can cause activation of the immune system. For example, acute stress induced by two brief public speaking stressors (Trier social stress test) has been shown to induce elevations in levels of the cytokine IL-6 (von Kanel et al., 2005, 2006), and an increase in the activity of NF-κB (Wolf et al., 2009). Similarly, rats exposed to

acute stress in the form of forced immobilisation (Sotnikov et al., 2009) or exposure to a brightly lit open field (LeMay et al., 1990) have demonstrated elevations in cytokine levels, particularly IL-6 (LeMay et al., 1990; Soszynski et al., 1997). In humans, chronic stress from sources such caring for a child with cancer (Miller et al., 2002) or a spouse with dementia (Kiecolt-Glaser et al., 2003) have been associated with elevations in cytokines and other inflammatory markers (Leonard and Myint, 2009). These findings extend to animal models of depression also, as exposure to the chronic mild stress paradigm (see Willner et al., 1987) has also been associated with an increase in pro-inflammatory cytokine release (Grippo et al., 2005).

3.1.7. Adaptive immunity in depression

In spite of the burgeoning literature regarding the role of the innate immune system in the pathogenesis and pathophysiology of depression, comparatively little evidence is available for the role of the adaptive immune system. To further complicate matters, there is significant disagreement over the interpretation of the existing data (for contrasting perspectives see Maes, 2010; Miller, 2010). A meta-analysis of the existing data on cellular immune function demonstrates a consistently reduced response of T cells from patients with depression to concanavalin A, pokeweed mitogen, and phytohaemagglutinin (Zorrilla et al., 2001). Several possible mechanisms may explain this association. The reduced availability of tryptophan due to induction of IDO as described earlier may reduce the function and increase the apoptotic rate of T cells (Mellor et al., 2003). Alternatively, the presence of soluble IL-2 receptors (sIL-2R) in the solution may reduce the effectiveness of the IL-2 dependent proliferative response (Eller et al., 2009; Caruso et al., 1993). It is relevant to note that sIL-2R has been demonstrated to be increased in patients with depression (Eller et al., 2009; Maes et al., 1995). Chronic exposure to high levels of TNF-α has also been demonstrated to impair T cell function (Clark et al., 2005).

The activity of T cells in depression is also a subject of intense speculation. While it is clear that peripherally active T cells secreting IFN-γ may contribute to the activation of further inflammatory responses (Maes, 2010), the function of autoreactive T cells in the CNS however may be more complex. Research over the past several years has demonstrated a possible neuroprotective role for T cells recognising self-antigen (Kipnis et al., 2004; Moalem et al., 2000; Schwartz and Shechter, 2010). This is, at least in part mediated by their ability to regulate BDNF levels (Lewitus et al., 2008). In addition to a neuroprotective role, studies have demonstrated that autoreactive T cells are required for maintenance of normal cognitive function (Schwartz and Shechter, 2010).

Some evidence also suggests a role for T regulatory (Treg) cells in the pathophysiology of depression. Treg cells have been shown to have neuroprotective effects as well (Ishibashi et al., 2009). Consistent with this, Treg have been demonstrated to increase following successful antidepressant therapy (Himmerich et al., 2010).

The balance between these T cell subtypes in both pathological and physiological conditions requires further investigation to unravel the complexity of their interactions before significant mechanistic interpolations can be made about their role in the neurobiology of depression.

3.2. Inflammation and T2DM

When studying the mechanisms and pathways of type 2 diabetes, it is important to recognise that it is difficult to dissect this disease process from the construct of 'metabolic syndrome'. This syndrome consists of diabetes or elevated fasting glucose levels, abdominal obesity, dyslipidaemia, and hypertension (Alberti et al., 2006). Of these components, obesity in particular may play a central role in mediating the relationship between inflammation and T2DM. Therefore while Table 3 lists studies suggesting a relationship between diabetes and inflammation, and other reviews compile similar lists associating obesity and inflammation, it is important to recognise that these are perhaps simply different perspectives on the same pathogenetic process. Table 3 lists prospective studies between 2006 and 2010 suggesting a relationship between inflammatory markers and T2DM. Studies published before 2006 are tabulated and summarised in an excellent review by Duncan and Schmidt (2006).

3.2.1. Obesity and inflammation

Adipose tissue was formerly regarded as purely a storage site for excess fatty acids, however a modern view suggests a far more complex role for this organ. Developments in recent years have uncovered an endocrine role for adipose tissue and its constituents, primarily through the release of adipokines, a collection of proteins with endocrine capabilities and the potential to influence metabolism, the immune system, and the vasculature. These adipokines are released from various cell types within the adipose tissue including vascular endothelium, resident macrophages, and the adipocytes themselves (Maury and Brichard, 2010). The process leading to an inflammatory state in the adipose tissue is not completely understood and several possibilities have been raised. These include the increase in NF-κB and JNK activity by hypertrophied adipocytes, endoplasmic reticulum stress resulting in activation of the 'unfolded protein response', hypoxic stress in adipose tissue, activation of toll-like receptor-4 (TLR4) by excess free fatty acids (FFA), or increased chylomicron mediated transport of LPS from the gut lumen into circulation in a lipid rich diet. A detailed discussion of these mechanisms is beyond the scope of this paper, however several recent reviews are available on these topics (Donath and Shoelson, 2011; Hotamisligil, 2010; Maury and Brichard, 2010).

After initiation of the inflammatory process, most likely through a combination of the above events, the potentiation of this response is primarily dependent on the actions of several cell types in adipose tissue and the liver. Larger adipocytes are known to shift their secretory activity towards an increase in pro-inflammatory adipokines, including monocyte chemoattractant protein-1 (MCP-1) (Skurk et al., 2007). MCP-1 results in an influx of macrophages of a pro-inflammatory phenotype, also known as M1 or 'classically activated'. This influx skews the balance in adipose tissue away from the M2 or 'alternatively activated', macrophages who also have the capability to secrete 'anti-inflammatory' cytokines (Lumeng et al., 2008). The net increase in secretion of inflammatory molecules further stimulates the secretion of pro-inflammatory molecules by hypertrophied adipocytes (Maury et al., 2009). In obese people, this shift in M1/M2 balance, coupled with increased overall macrophage density, and secretion from hypertrophied adipocytes results in an increase in the levels of 'pro-inflammatory' adipokines, and a decrease in levels of 'anti-inflammatory' adipokines. This alteration in adipokine profile may contribute to the insulin resistance that is characteristic of T2DM (Antuna-Puente et al., 2008; Maury and Brichard, 2010).

Circulating levels of several of these adipokines have been shown to correlate with obesity and many appear to have a role in obesity related insulin resistance. Table 4 lists *in vivo* studies of the effects of several of these adipokines on insulin resistance. It is also relevant to note that many of these adipokines have been shown to have activity in the CNS or at the BBB in addition to their peripheral effects (see for review Pan and Kastin, 2007).

In addition to adipose tissue, the primary tissues that are responsible for maintenance of glucose homeostasis in response to insulin are the liver and skeletal muscle. The establishment of a pro-inflammatory state in these three tissues may form the conditions for the systemic disruption of insulin sensitivity and glucose

Table 3
Prospective studies of the relationship between markers of inflammation and onset of diabetes.

Author/year	Study cohort	Incident diabetes definition	Sample	Proteins/markers investigated	Significant associations (fully adjusted)
Weng et al. (2010)	34–38 YO males and females with essential hypertension	FPG ≥ 126 mg/dl or HbA1c > 6%	Serum, plasma	hsCRP, adiponectin	hsCRP
Luft et al. (2010)	ARIC: 45–64 YO males and females	Self report, hypoglycaemic medication use, FPG ≥ 126 mg/dl or random glucose > 200 mg/dl	Plasma	DPP-IV	–
Chao et al. (2010)	WHIOS: 50–79 YO females	Self report or hypoglycaemic medication use	Plasma	WBC count, TNF-R2, IL-6, hsCRP, E-selectin, ICAM-1, VCAM-1	–
Carstensen et al. (2010)	Whitehall II: 41–64 YO males and females	Self report or hypoglycaemic medication use or FPG ≥ 126 mg/dl or OGTT (>200 mg/dl after 2 h)	Serum	IL-1ra	IL-1ra
Bertoni et al. (2010)	MESA: 45–84 YO males and females	FPG ≥ 126 mg/dl or hypoglycaemic medication use	Serum	Fibrinogen, hsCRP, IL-6	Fibrinogen, hsCRP, IL-6
Onat et al. (2009)	TARF: 35–80 YO males and females	FPG ≥ 126 mg/dl or OGTT (>200 mg/dl after 2 h)	Serum	ApoA-II	ApoA-II
Li et al. (2009)	Meta-analysis of studies published up to April 10, 2009	Variable	Plasma	Adiponectin	Adiponectin
Hivert et al. (2009)	NHS: 30–55 YO females	FPG ≥ 140 mg/dl or OGTT (>200 mg/dl after 2 h) or random glucose > 200 mg/dl or hypoglycaemic medication use	Plasma	IL-18, IL-6, CRP, TNF-R2, adiponectin, resistin	IL-18, IL-6, CRP, TNF-R2, adiponectin, resistin
Herder et al. (2009)	MONICA/KORA: 35–74 YO males and females	Physician diagnosis or hypoglycaemic medication in medical records	Serum	TGF-1β	TGF-1β
Chen et al. (2009)	WHS: ≥40 YO postmenopausal females PHS II: ≥55 YO males	Self report	Plasma	Resistin, TNF-R2, CRP	Resistin, TNF-R2, CRP
Wannamethee et al. (2008)	BRHS: 40–59 YO males	Self report validated by review of notes	Plasma	CRP, IL-6, vWF, t-PA	CRP, IL-6, vWF, t-PA
Stranges et al. (2008)	WNYHS: 35–79 YO males and females	Self report and hypoglycaemic medication use or FPG > 125 mg/dl	Serum or plasma	hsCRP, IL-6, PAI-1, ICAM-1, E-selectin, adiponectin, fibrinogen, albumin, WBC count	hsCRP, PAI-1, E-selectin, adiponectin, fibrinogen, albumin, WBC count
Perticone et al. (2008)	22–60 YO males and females with essential hypertension	Symptomatic and (FPG ≥ 126 mg/dl, or random glucose ≥ 200 mg/dl or OGTT [>200 mg/dl after 2 h]) and hypoglycaemic medication use	Serum	CRP	CRP
Herder et al. (2008b)	MONICA/KORA: 35–74 YO males and females	Physician diagnosis or hypoglycaemic medication in medical records	Serum	Serum MIF, MIF genotype	Serum MIF, several MIF haplotypes and SNP (see study for details)
Herder et al. (2008a)	MONICA/KORA: 35–74 YO males and females	Physician diagnosis or hypoglycaemic medication in medical records	Serum	Serum RANTES/CCL5 and CCL5 genotype	–
Wannamethee et al. (2007)	BRHS: 40–59 YO males	Self report validated by review of notes	Plasma	Leptin, adiponectin, IL-6	Leptin, adiponectin, IL-6
Wang and Hoy (2007)	20–74 YO males and females	Review of hospital and clinic records	Serum	hsCRP	hsCRP
Thorand et al. (2007b)	MONICA/KORA: 35–74 YO males and females	Physician diagnosis or hypoglycaemic medication in medical records	Serum	CRP, IL-6	CRP, IL-6
Thorand et al. (2007a)	MONICA/KORA: 35–74 YO males and females	Physician diagnosis or hypoglycaemic medication in medical records	Serum	CRP, IL-6, IL-18, ICAM-1, E-selectin, sTM	CRP, IL-6, IL-18, ICAM-1, E-selectin, sTM (inverse association)
Liu et al. (2007)	WHIOS: 50–79 YO females	Self report or hypoglycaemic medication use	Serum and plasma	TNF-R2, hsCRP, IL-6	hsCRP, IL-6
Hoogeveen et al. (2007)	ARIC: 45–64 YO males and females	Self report, hypoglycaemic medication use, FPG ≥ 126 mg/dl or random glucose > 200 mg/dl	Plasma	Oxidised-LDL, ICAM-1	Oxidised LDL, ICAM-1
Forouhi et al. (2007)	EPIC-Norfolk: 40–74 YO males and females	Self report or hypoglycaemic medication use or HbA1c > 7% or review of notes	Serum	Ferritin	Ferritin
Dehghan et al. (2007)	Rotterdam Study: ≥55 YO males and females	GP diagnosis or hypoglycaemic medication use, FPG ≥ 126 mg/dl or random glucose > 200 mg/dl	Serum	hsCRP	hsCRP
Kanaya et al. (2006)	Health ABC: 70–79 YO males and females	Self report or hypoglycaemic medication use or FPG ≥ 126 mg/dl	Serum	IL-6, TNF-α, PAI-1, leptin, adiponectin	PAI-1

Herder et al. (2006c)	Finnish DPS: 40–65 YO males and females	FGP ≥ 140 mg/dl or OGTT (>200 mg/dl after 2 h)	Serum	ICAM-1, MIF, RANTES, IL-6, CRP, SAA	CRP, RANTES
Herder et al. (2006b)	KORA: 55–74 YO males and females	FGP ≥ 126 mg/dl or OGTT (>200 mg/dl after 2 h)	Serum	MIF, CRP, IL-6	MIF, CRP, IL-6
Herder et al. (2006a)	MONICA/KORA: 35–74 YO males and females	Physician diagnosis or hypoglycaemic medication in medical records	Serum	MCP-1, IL-8, IP-10	MCP-1
Festa et al. (2006)	IRAS: 40–69 YO males and female	OGTT (>200 mg/dl after 2 h)	Plasma	Fibrinogen, PAI-1	Fibrinogen, PAI-1

YO: years old; hsCRP: high sensitivity C-reactive protein; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin; ARIC: the atherosclerosis risk in communities study; DPP-IV: dipeptidyl peptidase IV; WHIOS: the women's health initiative observational study; TNF-R2: tumour necrosis factor receptor-2; IL: interleukin; WBC: white blood cell; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; OGTT: oral glucose tolerance test; MESA: the multi-ethnic study of atherosclerosis; ApoA-II: apolipoprotein A-II; TARF: Turkish adult risk factor study; NHS: the nurses' health study; MONICA/KORA: monitoring of trends and determinants in cardiovascular disease/cooperative health research in the region of Augsburg cohort; TGF-1β: transforming growth factor-1β; WHS: women's health study; PHS II: physician's health study II; BRHS: British regional heart study; vWF: von Willebrand factor; t-PA: tissue plasminogen activator; PAI-1: plasminogen activator inhibitor-1; MIF: macrophage migration inhibitory factor; SNP: single nucleotide polymorphism; RANTES/CCL5: regulated on activation normal T-cell expressed and secreted/chemokine CC motif 5; sTM: soluble thrombomodulin; LDL: low density lipoprotein; EPIC: European prospective investigation of cancer; GP: general practitioner; Health ABC: health ageing and body composition study; DPS: diabetes prevention study; SAA: serum amyloid A; MCP-1: monocyte chemoattractant protein-1; IP-10: interferon-γ inducible protein-10; and IRAS: the insulin resistance in atherosclerosis study.

homeostasis that is characteristic of T2DM (Brun et al., 2007; Hijona et al., 2010; Varma et al., 2009).

3.2.2. Obesity and inflammation leading to T2DM

The establishment of a pro-inflammatory state in these tissues results in the activation of several intracellular signalling cascades including JNK, AP-1, and the IκB kinase-β (IκK-β)-NF-κB pathway. Serine kinases from these pathways interact with insulin receptor substrates (IRS) by phosphorylating and therefore inactivating them. In the absence of this inhibition, insulin receptor tyrosine kinases would activate these IRS, which in turn would activate the two major insulin signalling pathways – the MAPK pathway and the phosphatidylinositol 3-kinase-Akt (PI_3K-Akt) pathway. Inactivation of IRS leads to a loss of insulin dependent stimulation for these pathways, however it is important to recognise that there are other pathways of insulin signal transduction not associated with IRS (Zeyda and Stulnig, 2009). Additionally, endoplasmic reticulum stress (induced by excess anabolic activity) has been shown to downregulate expression of the insulin dependent glucose transporter GLUT4 in adipocytes (Miller et al., 2007). Beyond these general mechanisms, each of the adipokines listed in Table 4 has specific interactions with insulin or glucose homeostasis. In addition to the activation of the above pathways, the cytokine/adipokines IL-6 and TNF-α also activate the suppressor of the cytokine signalling (SOCS)3 molecule. The SOCS1 and SOCS3 molecules appear to be primarily responsible for providing negative feedback to the JAK-STAT pathway used for the intracellular signalling of certain cytokines and they also appear to play a role in the inhibition of insulin's intracellular signalling cascades through antagonism of both the insulin receptor and IRS (Emanuelli et al., 2001). Also, SOCS molecules may induce ubiquitinlyation of IRS marking them for proteosomal degradation (Rui et al., 2002).

Patients with T2DM not only show signs of insulin resistance, but also impaired activity of pancreatic β-cells including increased rates of β-cell apoptosis. This apoptosis is believed to be primarily induced by glucotoxicity and lipotoxicity (Lupi and Del Prato, 2008).

3.2.3. T2DM leading to inflammation

A diabetic state is be characterised by insulin resistance and recurrent hyperglycaemia, and both of these facets have the potential to contribute to systemic inflammation. The insulin resistant state is accompanied by hyperinsulinaemia, and interestingly some authors have described anti-inflammatory properties of insulin. A series of papers published by Dandona et al. over several years supports the position that insulin is capable of reducing the activity of NF-κB, and therefore disrupting the transcription of several key inflammatory mediators (Dandona et al., 2009). Recently, Iwasaki et al. put forward that insulin may exert anti-inflammatory effects in the short term, but chronic exposure could result in a pro-inflammatory effect via inhibition and stimulation of NF-κB respectively (Iwasaki et al., 2009). Regardless of the uncertainty surrounding the role of insulin in inflammation, there is a wealth of literature on the pro-inflammatory effects of hyperglycaemia. In brief, hyperglycaemia causes increased mitochondrial production of ROS leading to strand breaks in DNA. As part of the repair process, the protein poly(ADP-ribose) polymerase is activated. This protein modifies a key enzyme in the pathway of glycolysis (glyceraldehyde-3 phosphate dehydrogenase) by adding polymers of ADP-ribose to it. In this state, the enzyme has a reduced activity resulting in the accumulation of upstream intermediates in the glycolytic pathway. These intermediates activate four key pathways that lead to immune activation: reduced synthesis of the antioxidant glutathione, an increase in the synthesis of advanced glycation endproducts (AGEs), disruption of several transcription factors by N-acetyl glucosamine binding, and activation of protein kinase C (PKC) (see for review Brownlee, 2005). PKC has the

Table 4
In vivo effects of adipokines on insulin sensitivity.

Author/year	Treatment	Test	Sample	Protein	Main findings
Hotamisligil et al. (1993)	TNF-α applied to cultured adipocytes	Northern Blot	Adipocyte	TNF-α	Chronic treatment of adipocytes with TNF-α reduced GLUT-4 expression
	IP Anti-TNF-α IgG	Hyperinsulinemic-euglycaemic clamp	Plasma		TNF-α neutralisation increases insulin sensitivity *in vivo*
Holmes et al. (2008)	IL-6 either chronically through osmotic pumps or through twice daily IP injections	GTT and ITT	Plasma	IL-6	HOMA-IR analysis demonstrated a decreased insulin resistance and increased glucose tolerance in both treatment groups compared to controls
Klover et al. (2003)	IL-6 through an osmotic pump	ITT	Serum	IL-6	IL-6 treated mice had significantly higher insulin resistance
		Western Blot	Liver and skeletal muscle		Hepatic insulin receptor signalling was inhibited in IL-6 treated mice but not in skeletal muscle
Del Rey et al. (2006)	Administration of central or peripheral IL-1 and/or IL-1ra to wild type, db/db, or db/+ mice	GTT	Serum and brain tissue	IL-1	IL-1 induces hypoglycaemia through central actions that are independent of insulin and counter-regulatory hormones
Steppan et al. (2001)	IP resistin or anti-resistin IgG	GTT	Serum	Resistin	Resistin administration suppresses insulin sensitivity both *in vivo* and *in vitro*
	Cultured adipocytes were exposed to resistin or anti-resistin IgG	[^{3}H]2-deoxyglucose uptake assay	Adipocyte		Anti-resistin IgG potentiates the activity of insulin *in vivo* and *in vitro*
	Rosiglitazone – route not specified	Western Blot	Serum		Rosiglitazone treatment reduces serum resistin levels
Revollo et al. (2007)	Nampt was injected IP	Serum glucose level	Serum	Visfatin/Nampt	Nampt does not reduce blood glucose levels *in vivo*
	Nampt+/− mice generated	GTT	Serum		Nampt+/− mice demonstrate impaired glucose tolerance and reduced glucose stimulated insulin secretion
	Nampt applied to cultured adipocytes	Western Blot and [^{14}C]2-deoxyglucose assay	Adipocyte		Nampt does not show any effect on glucose uptake in cultured adipocytes and does not interact with insulin receptors or Akt
Oral et al. (2002)	Leptin was administered to patients with lipodystophy and diabetes for four months	GTT and ITT	Serum	Leptin	Treatment with leptin replacement therapy improved insulin sensitivity and glucose tolerance
Yamauchi et al. (2001)	Adiponectin administered IP to db/db, KKA^y, and lipoatrophic mice	GTT and ITT	Serum	Adiponectin	Serum adiponectin levels were reduced in db/db, KKA^y and lipoatrophic mice which correlated with reduced insulin sensitivity compared to controls. Adiponectin replacement increased insulin sensitivity
Hida et al. (2005)	Mice fed a high fat, high sucrose diet to develop obesity were treated with Vaspin	GTT and ITT	Serum	Vaspin	Vaspin treatment ameliorated the obesity associated insulin resistance and gene expression profile of white adipose tissue – reducing expression of leptin, resistin, and TNF-α while increasing expression of GLUT-4 and adiponectin
		RT-PCR and genechip analysis	Adipocyte		

Dray et al. (2008)	Apelin was administered IV to high fat fed obese and non-obese mice	GTT and hyperinsulinemic-euglycaemic clamp	Serum and plasma	Apelin	Apelin increased glucose tolerance, glucose turnover, and peripheral glucose utilisation in both obese and non-obese mice
Becker et al. (2010)	Chemerin was overexpressed in high fat fed LDL receptor −/− mice using a recombinant adeno-associated virus	GTT and ITT	Plasma	Chemerin	Chemerin overexpressing mice demonstrated impaired glucose tolerance and insulin sensitivity
		Western Blot	Liver, skeletal muscle, adipose tissue		Chemerin impaired insulin signalling pathways in skeletal muscle but not adipose tissue or liver
Lijnen et al. (2005)	Aged PAI-1 overexpressing mice and age-matched controls were either given PAI-1 inhibitor containing food or standard food	GTT and ITT	Plasma	PAI-1	Fasting insulin levels were significantly higher in PAI-1 overexpressing mice
					Fasting glucose levels were significantly lower in PAI-1 overexpressing mice receiving PAI-1 inhibitor Wild type mice receiving PAI-1 inhibitor had a significantly increased insulin sensitivity GTT and ITT were similar between genotypes
Yang et al. (2005)	Serum RBP-4 levels were determined in adipose tissue specific GLUT-4 −/−, high fat fed, and ob/ob mice, obese-diabetic ad nonobese-diabetic patients	Western Blot	Plasma or serum	RBP-4	Adipose tissue specific GLUT-4 −/−, high fat fed, and ob/ob mice, obese-diabetic ad nonobese-diabetic patients had elevated levels of serum RBP-4 compared to their respective controls
	Rosiglitazone was administered to a group of GLUT-4 −/− mice	Western Blot	Plasma or serum		Rosiglitazone reversed the RBP-4 elevation in adipose tissue specific GLUT-4 −/− mice
	RBP-4 −/− and RBP-4 overexpressing mice were generated	GTT and ITT	Plasma		Both RBP-4 overexpressing mice and mice injected with RBP-4 demonstrated increased insulin resistance
	A cohort of wild type mice were injected with RBP-4	GTT and ITT	Plasma		RBP-4 −/− mice and obese mice where RBP-4 was eliminated by feretinide treatment demonstrated increased insulin sensitivity
	A cohort of both obese and non-obese mice was treated with feretinide	GTT and ITT	Plasma		Post-insulin receptor signalling was reduced in the skeletal muscle but not liver of RBP-4 overexpressing mice, mice given IP injections of RBP-4
		Skeletal muscle and liver from all mice was analysed for post-insulin receptor signalling	Skeletal muscle and liver		Post-insulin receptor signalling was increased in skeletal muscle but not liver of GLUT-4 −/− and feretinide treated mice

−/−: knockout; IP: intra-peritoneal; IV: intra-venous; GTT: glucose tolerance test; ITT: insulin tolerance test; RT-PCR: reverse transcriptase polymerase chain reaction; LDL: low density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; IgG: immunoglobulin isotype G; PAI-1: plasminogen activator inhibitor-1; and RBP-4: retinol binding protein-4.

potential to upregulate the expression of PAI-1, and also increase the activity of NF-κB which will itself increase the expression of pro-inflammatory gene products such as TNF-α and IL-6. ROS also increase the expression of the receptor for AGEs (RAGE), which when ligated results in the activation of several intracellular signalling cascades relevant to inflammation including NF-κB and AP-1 (Yao and Brownlee, 2010). Of particular interest, RAGE activates NAD phosphate oxidase and increases the production of ROS, possibly contributing to a positive feedback loop (Wautier et al., 2001). However, AGEs are not the only ligand for RAGE. Advanced oxidation protein products, advanced lipoxidation end products, S100/calgranulins, high mobility group box-1, and amyloid-β peptide may all bind and activate RAGE in various circumstances (Yao and Brownlee, 2010). Another effect of hyperglycaemia is the induction of an increase in TLR-2 and TLR-4 expression on monocytes. This is particularly relevant to the potentiation of an inflammatory response in a patient with both obesity and T2DM as the ligands for these receptors include FFA and AGE (Dasu et al., 2008).

3.2.4. Adaptive immunity in obesity and T2DM

Little is known about the role of adaptive immunity in obesity-related adipose tissue inflammation. Studies have shown that adipose tissue contains resident T cells, and that the characteristics of this resident population change with increasing obesity. Animal models of obesity and insulin resistance have demonstrated a shift in the TH2/TH1 balance in favour of TH1, shift of the CD8/CD4 ratio towards CD8 (Nishimura et al., 2009), skew of the Treg/TH17 balance towards TH17 (Feuerer et al., 2009; Winer et al., 2009), and a reduction in T-cell receptor (TCR) diversity (Yang et al., 2010). These findings have recently been extended to human studies (Jagannathan-Bogdan et al., 2011). This is consistent with an activation of a TH1 type response to ongoing antigen exposure resulting in an increase of pro-inflammatory stimuli (IFN-γ) that may contribute to activation of adipose tissue macrophages to the M1 phenotype (Yang et al., 2010). Reciprocally, the hyperactivity of the pro-inflammatory T cell populations observed in these patients appears to be dependent on the presence of macrophages/monocytes of a pro-inflammatory phenotype (Jagannathan-Bogdan et al., 2011). In addition to contributing to a pro-inflammatory positive feedback loop with the innate immune cells, IFN-γ and IL-17 produced by these T cell populations may interact directly with adipocytes. IL-17 has been demonstrated to induce IL-6 secretion from adipocytes (Shin et al., 2009), and IFN-γ inhibits the JAK-STAT pathway as discussed above (McGillicuddy et al., 2009). Furthermore, there is some evidence to suggest the occurrence of obesity cell activation in samples from patients with T2DM and obesity. One study has demonstrated an increase of IL-8 secretion and decrease of IL-10 secretion in B cells isolated from these patients (Jagannathan et al., 2010).

4. The bidirectional relationship between depression and T2DM

4.1. T2DM leading to depression

The increase in pro-inflammatory mediators detailed above provides a plausible mechanistic link explaining the increased incidence of depression among patients with T2DM. It is important to note that T2DM is commonly associated with increased adiposity or obesity, a factor that has independently been associated with depression (Luppino et al., 2010). Given the existence of inflammatory pathways with the potential to inter-relate these three conditions, it appears possible that these observed relationships may indeed be causal. A diabetes and/or obesity related increase in inflammatory markers, hyperglycaemia and possibly hyperinsulinaemia may contribute to a net pro-inflammatory state in many tissues. Access of pro-inflammatory mediators to the CNS may then lead to an activation of the pathways leading to the development of depressive symptoms as reviewed above. An animal study demonstrated in the db/db mouse model of diabetes that both the central and peripheral anti-inflammatory feedback responses to IL-1β or LPS were reduced in diabetic mice. This correlated with a significant extension of the 'sickness behaviour' responses in the diabetic mice (O'Connor et al., 2005). In addition, T2DM is associated with reduced volumes in areas of the brain implicated in depression such as the hippocampus and amygdala, providing strong support for the suggestion that T2DM does provide a true biological risk factor for depression (McIntyre et al., 2010a). Also, an animal model of T2DM (db/db mouse) has recently been found to exhibit a depressive phenotype in the forced swim test (Sharma et al., 2010). Although this review has focussed on the biological pathways between depression and T2DM, it is important to note that the psychosocial implications of diabetes and diabetic complications may also play a role in the later development of depression. It has been suggested that the stress of a diagnosis of diabetes may predispose to the onset of depression, however several of the studies in Table 1 demonstrate an association of undiagnosed T2DM with depressive symptoms indicating that this alone is not sufficient to explain the relationship (Musselman et al., 2003).

4.2. Depression leading to T2DM

The epidemiological observation that depression increases the risk for a subsequent development of T2DM may also be explained through inflammatory pathways. An increase in the central synthesis of pro-inflammatory mediators, including IL-1β, TNF-α, and IL-6 may contribute to systemic inflammation as these cytokines are able to cross the BBB into the circulation (Banks et al., 1989; Gutierrez et al., 1993). These mediators have the potential to interact with insulin sensitivity and pancreatic β-cell function to contribute to the development of T2DM as detailed above. Indeed, an animal model of astrocyte specific IL-6 overexpression found that when combined with a high fat diet these mice were more glucose intolerant than their wild-type littermates, although their body weight was not affected (Hidalgo et al., 2010). Individuals with obesity are at an increased risk of developing T2DM, and consistent with this notion the interaction of mediators from the CNS with adipose tissue may contribute to an amplification of pro-inflammatory signalling from adipose tissue. TNF-α and IL-6 are both reliably correlated with depression, and may also regulate the production of several adipokines (Dowlati et al., 2010; Rabe et al., 2008). In addition, depression is associated with high levels of glucocorticoid production and glucocorticoid resistance which may further contribute to an inflammatory state through a loss of suppression of immune cells. Glucocorticoids are also a key counter-regulatory hormone to the actions of insulin on glucose homeostasis, primarily through a stimulation of hepatic gluconeogenesis and inhibition of glucose uptake by tissues. It is unclear whether the glucocorticoid resistance commonly found in immune cells extends to these metabolic actions (Musselman et al., 2003). Beyond these biological mechanisms, it is again important to stress that psychosocial and behavioural effects of depression may contribute to the later development of T2DM. It is also particularly poignant at this point to note the literature that has found poorer outcomes and an increased risk of diabetic complications among patients with co-morbid depression (Gendelman et al., 2009; Katon et al., 2009; Koopmans et al., 2009; Le et al., 2006; Lin et al., 2009, 2010; Maraldi et al., 2007; Molife, 2010; Musselman et al., 2003; Thaneerat et al., 2010; Winkley, 2008). It is tempting to speculate that patients with co-morbid depression may have a greater elevation in

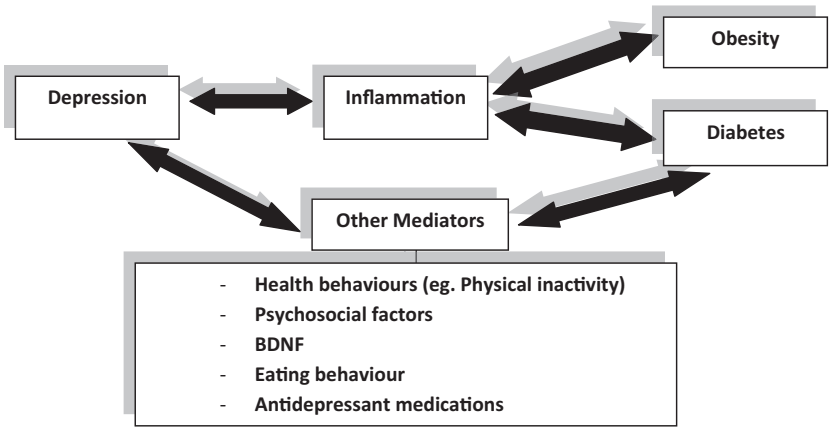

Fig. 3. The interrelationship between depression, diabetes, and inflammation.

pro-inflammatory mediators than non-depressed patients with T2DM, thereby increasing vulnerability to complications, however recent literature does not support this conclusion (Carnethon et al., 2007; Golden et al., 2008).

Alternatively, several other factors have been identified that may act as mediators of this relationship. These include poorer adherence to treatment and self-care activities (Yang et al., 2009), poorer metabolic control (Thaneerat et al., 2010), and exposure to the potential metabolic side effects of antidepressant medications.

The use of antidepressant pharmacotherapy is frequently considered as a mediator of the relationship between depression and T2DM. Several studies have found that certain antidepressant medications are associated with long term weight gain, and suggested that this may represent a key biological factor, however a recent meta-analysis found that the effects of antidepressants on glucose control remain ambiguous (van der Feltz-Cornelis et al., 2010). This may be due to significant heterogeneity in the pharmacological mechanisms of various antidepressant drugs (McIntyre et al., 2010b). Similarly, the effects of antidepressants on other aspects of metabolic disturbance such as weight gain and dyslipidaemia appears to be closely related to the specific antidepressant evaluated in each study (McIntyre et al., 2010b; Serretti and Mandelli, 2010). Although this body of literature does demonstrate an association of some antidepressant medications with the later onset of T2DM, this alone does not explain the observed association between the two conditions (Pyykkonen et al., 2011). Additionally, several of the studies listed in Table 1 demonstrate an association between undiagnosed, medication-free patients with depression or depressive symptoms and an increased incidence of T2DM.

5. Discussion

This review is the first to systematically draw together the literature supporting a role for inflammation as a mechanistic link in the co-morbidity between depression and T2DM. This review proposes a mechanistic model in which inflammation is a key factor in the bi-directional relationship between depression and T2DM (Fig. 3). As may be seen from the above tables, the relationship between these two conditions does appear bi-directional (Table 1) and inflammation is associated with both depression (Table 2) and T2DM (Table 3). Furthermore, the mechanisms discussed above provide putative pathways linking T2DM and depression, which is well supported by animal models. In summary, the epidemiological and mechanistic evidence reviewed above supports the hypothesis that inflammation may be involved with each stage of the bi-directional relationship between these conditions.

While exciting, the above discussion comes with several significant caveats. Firstly, despite the number of studies prospectively assessing the relationship between depression and T2DM (Table 1), only three of these have included measurement of inflammatory biomarkers (Carnethon et al., 2007; Golden et al., 2008; Maraldi et al., 2007). The measurement of biomarkers is key to advancing the mechanistic understanding of this relationship, however rigorous attention must also be paid to other potential mediators of this relationship including behavioural factors such as self care activities, treatment compliance, eating behaviours and the potential metabolic hazards of certain antidepressant medications. Secondly, the list of prospective studies investigating the relationship between depression and inflammation is quite brief and inconsistent (Table 2). This body of literature is also burdened by on over-representation of geriatric study samples, potentially limiting the relevance of this evidence to other populations. Other limitations include those common to all psychiatric research, namely the great variability in methods of psychiatric assessment and the inherent difficulty in establishing valid animal models. While the latter may be somewhat ameliorated by the current approach of modelling individual symptoms or symptom clusters, the entire field would benefit from the development of enhanced models and tests to improve the validity and reproducibility of these studies.

This is in stark contrast to the robust literature regarding the relationship of T2DM and inflammation (Table 3). In this area, both the human and animal literature benefits from many years of high quality interdisciplinary research (Tables 3 and 4). Indeed, while many controversies remain regarding the role of inflammation and adipokines as mediators of the relationship between T2DM and obesity, recent years have witnessed the emergence of the term 'diabesity' in recognition of the strength of evidence behind this association.

While this paper sets out an extensive mechanistic network that may provide a biological explanation for this co-morbidity, and these mechanisms are supported by good evidence in depression and 'diabesity' respectively, it is important to recognise that direct, high quality, prospective, human evidence to support a significant role for these mediators in the relationship between depression and 'diabesity' is lacking. In spite of this fact, this co-morbidity provides a promising area for future research with tangible translational benefits in the areas of prevention and treatment.

It may be of particular interest to note, that patients with co-morbid T2DM, obesity, and depression may be good candidates for novel anti-inflammatory pharmacotherapy. Current trials of anti-inflammatory agents for the treatment of depression have shown promising results, and further developments in this area are an exciting prospect. Clinical trials of cyclooxygenase-2 inhibitors

have demonstrated therapeutic efficacy for the treatment of depression (Muller et al., 2006). Additionally, the TNF-α antagonist etanercept has demonstrated efficacy in reducing depressive symptoms in patients with psoriasis (Tyring et al., 2006). Anakinra, the recombinant human form of IL-1ra also has demonstrated a significant effect in clinical trials for the treatment of T2DM (Larsen et al., 2007). Interventions targeting adaptive immune processes may also hold promise, although they have not progressed to human trials. In animal models, a targeted induction of Treg cells has demonstrated efficacy in improving insulin sensitivity, glucose homeostasis, and adipose tissue inflammation (Feuerer et al., 2009; Ilan et al., 2010). A meta-analysis of clinical trials of the current treatments for co-morbid T2DM and depression suggests that the most effective intervention for these patients is combined psychotherapy and diabetes education. This was demonstrated to significantly improve both depressive symptoms and glycaemic control, however it is not possible to discern from these studies whether the interventions have a synergistic effect (van der Feltz-Cornelis et al., 2010).

In the preventative arena, an extended understanding of this co-morbidity may provide a deeper biological understanding of the well-established benefits of exercise, diet and omega-3 polyunsaturated fatty acids in the prevention of depression and T2DM. Additionally, it may provide a target for the implementation of novel preventative strategies as recognition of their emerging anti-inflammatory properties.

6. Conclusion

This paper has detailed current evidence and possible mechanisms of an inflammatory link between depression and T2DM. Currently, there is an urgent need for more prospective studies of this co-morbidity including the assessment of inflammatory biomarkers. Further prospective studies on the relationship between depression and inflammation are also needed to strengthen this evidence base.

The co-morbidity of depression and T2DM presents not only a significant challenge, but also a significant opportunity to healthcare professionals in both clinical and research domains. Through advancing the understanding of the mechanistic links that mediate this relationship, new avenues for research, treatment, and prevention of these conditions may become clear.

Acknowledgement

The authors would like to thank Harris Eyre for his assistance with the initial data collection process.

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