



Review

Type 2 diabetes mellitus, drug addiction, bipolar disorder and epilepsy display overlapping aetiopathogenic mechanisms: Implication for prevention and pharmacotherapy

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Abstract

The prevalence of diabetes and co-morbid diseases, especially in developing countries, may have already exceeded estimates. Accumulating reports indicate considerable underpinnings in the mechanisms of the aetiopathogenesis of metabolic syndrome, bipolar disorder, epilepsy and, recently, substance addiction. Continuing evidence incriminates dysfunction in genetic, mitochondrial and inflammatory cascade mechanisms as contributory factors to the dysregulation of neurotrophic, serotonergic, dopaminergic, adrenergic, glutamatergic, GABAergic and autophagic pathways. There may also be co-incident dysregulation of the global anti-oxidant network, the endogenous digitalis system, the vasopressin signalling and the hypothalamo-pituitary-adrenal axis. Nuclear factor-kappa B (NF-kappa B) signaling and reactive oxygen species lead to activation of the mammalian target of rapamycin complex I (mTORC1) and this process may be central to the aetiopathogenesis of drug addiction, obesity, foetal programming, diabetes mellitus, epilepsy and bipolar disorder. Anti-glycaemics such as cannabinoid CB2 agonists, metformin, artesunate and valproate; insulin-mimetics such as glucagon-like peptide-I (GLP-I) and its analogues; phytomedicines from garlic and curcumin are now shown to exhibit neuroprotective effects. These agents which may down-regulate inflammatory cytokines, upregulate endothelial nitric oxide (eNOS) and peroxisome proliferator-activated receptor alpha (PPAR- α) signalling, attenuate mitochondrial dysfunction, enhance the actions of glucagon-like peptide-I (GLP-I), inhibit mTOR, NF-kappa B, interleukin-1 β and glycogen synthase kinase-3 β stand to be of benefit in these illnesses which demonstrate considerable overlap in their aetopathogenic mechanisms. Underpinnings and bidirectional relationships between the metabolic syndrome and mental health disorders may pave way for common new fronts to drug development in translational cardiovascular psychiatry and neurology.

Keywords: Metabolic syndrome, Bipolar disorder, Drug Addiction, Epilepsy, Mechanisms, Overlap

INTRODUCTION

Globally, type 2 diabetes mellitus is increasing in epidemic proportions (King and Rewers, 1991). According to WHO, the prevalence of diabetes mellitus in adults worldwide was estimated to be 4.0% in 1995 and

is predicted to rise to 5.4% by the year 2025. This means the number of adults with diabetes mellitus in the world would rise from 135 million in 1995 to 300 million in the year 2025. Additionally, hypertension affects one billion

people worldwide and it is estimated that by 2025, up to 1.56 billion adults worldwide will be hypertensive. There is an association between hyperinsulinaemia and essential/genetic hypertension but not with secondary hypertension (El-Atat et al., 2004).

Diabetes and hypertension exert a significant burden resulting in increased morbidity and mortality (Moller, 2001), decreased life expectancy and reduced quality of life. For example, according to WHO, the life expectancy of Nigerians fell from 51-56 years in 2000 to 47.56 years in 2011 due to the epidemic of the metabolic or insulin resistance syndrome (Mohan et al., 2013; Awosan et al., 2013; Udenze et al., 2013). In tandem, the prevalence of epilepsy (Osuntokun et al., 1987; Olubunmi, 2006) and of drugs of abuse in Nigerians (Chikere and Mayowa, 2011; Ekpeyong, 2012), factors that may upregulate the inflammatory cascade, may also be on the upward trend.

Investigators have reported links between bipolar disorder, the insulin resistance syndrome, obesity and drug addiction (D'Mello et al., 2010; Kemp and Fan, 2012; Nousen et al., 2013; Kenny, 2011; Baik, 2013). The rate of the metabolic syndrome in bipolar disorder varies from 17% to 67% depending on sample size (Grover et al., 2012). Evidence suggests that (molecular) defects associated with the development of diabetes also contribute to an increased risk of all types of neuropsychiatric illnesses including affective disorders (Nousen et al., 2013; Wahlqvist et al., 2012; Cole et al., 2007). This could represent a pathway for new drug development with the biguanide metformin and some phytomedicines (Licinio J, 2011; Stein D, 2012; Berk, 2012; Wahlqvist et al., 2012; Patel et al., 2012).

Additionally, hypoxia-dependent amyloidogenesis, a sequelae of hypertension, could lead to Alzheimer's disease, creating the cerebrovascular-Alzheimer's disease spectrum that may be responsive to some anti-hypertensives such as carvedilol and valsartan that have neuroprotective effects (Wanget al., 2011; Jin et al., 2014; Valenzuela et al., 2012; Alexander et al., 2011; Wang et al., 2007).

These revelations point to new, unsuspected association of cardiovascular disorders with bipolar mood disorders (Manev, 2009_A, 2009_B, Skaper et al., 2009; Yanev et al., 2013; Nichols, 2009; Omar et al., 2012). The possible mediators of this association, such as polymorphism in the matrix metalloproteinase-9 (MMP9) gene (Rybakowski, 2009), microRNA-regulated pathways (Zhu et al., 2013; Hebert, 2009) and dysfunction in eNOS signalling (O'Sullivan et al., 2014), are being unravelled. Immune/inflammatory and cardiometabolic risk factors may be common endophenotypes of both physical and psychiatric illnesses including drug addiction (Krishnadas et al., 2014; Kovacs, 2012; Kenny, 2011; McIntyre et al., 2009). Importantly, the metabokines ATP-NGF and BDNF are now known to mediate trophobiological effects through immunotrophic to metabotrophic effects involved in pathogenesis of various neuropsychiatric and

metabolic diseases when dementia, depression, type 2 diabetes and obesity may express a common phenotype and existence (Gray et al., 2006; Li, 2007; Chaldakov et al., 2009; 2014; Yanev et al., 2013). NGF and BDNF are involved in synaptogenesis and pancreatic β -cell survival. Included in the list of selected NGF- and BDNF-related diseases are obesity, metabolic syndrome, atherosclerosis, bipolar spectrum disorders, eating disorders, diabetic neuropathy and retinopathy, epilepsy and Alzheimer's disease.

Metabolic Syndrome

Metabolic syndrome is a cluster of cardiometabolic risk factors which include insulin resistance, prediabetes, type 2 diabetes mellitus, central obesity, dyslipidaemia, hypertension, atherosclerotic cardiovascular disease, hypercoagulability and microalbuminuria (WHO, 1999; Alberti et al., 2005; El-Atat et al., 2004; Awosan et al., 2013).

High-fat diet and obesity may be linked to type 2 diabetes mellitus and epilepsy through the Notch signalling pathway (Li et al., 2013; Liu et al., 2014), thus creating the diabetes spectrum (Chaldakov et al., 2014). Inhibition of Notch signalling pathway promotes browning of white adipose tissue by increasing number of beige fat cells which improves glucose homeostasis (Bi et al., 2014; Li et al., 2013). Interleukin 4/13 induction and M2 macrophages activation are required for biogenesis of beige fat (Qiu et al., 2014; Rao et al., 2014). In addition, targeted disruption of transforming growth factor-beta (TGF- β) superfamily receptor, activin receptor-like kinase 7 (ALK7), alleviates diet-induced catecholamine resistance in adipose tissue, thereby reducing obesity (Guo et al., 2014). Obesity may also be linked to type 2 diabetes by an absent protein, nuclear ubiquitous casein and cyclin-dependent kinase substrate (NUCKS). NUCKS is a positive transcriptional regulator of insulin signalling (Qui et al., 2014) and works by regulating chromatin and RNA polymerase II recruitment to the promoters of insulin receptor and other insulin pathway modulators. NUCKS is down-regulated in individuals with a high body mass index and in high fat fed mice. Its levels increase upon starvation. Additionally, variants of the demethylase, the fat mass and obesity-associated (FTO) gene (Fraying et al., 2007) have been positively correlated with obesity, metabolic syndrome and Alzheimer's disease in humans. In the same vein, high fat diet feeding which can also be induced by drugs of abuse such as morphine (Will et al., 2006) produces brain insulin resistance, synaptodendritic abnormalities and altered behaviour in mice (Arnold et al., 2014). It also reduces brain neuropeptide Y, brain-derived neurotrophic factor and cyclic adenosine monophosphate response element binding protein levels with reduced cell proliferation and neuroblast differentiation in the dentate

gyrus (Yoo et al., 2011; Azoulay et al., 2008). High fat diet also increases blood uric acid levels and reduces brain docosahexaenoic acid levels (Sharma et al., 2014). Elevated serum uric acid is a strong predictor of the development of the metabolic syndrome (Choi et al., 2014) and impulsivity (Sutin et al., 2014). Uric acid, which upregulates the sterol regulatory element binding protein (SREBP-1c) (Choi et al., 2014), may be a biological marker for the differentiation of unipolar and bipolar disorders (Kesebir et al., 2014). Its levels are increased in drug-naïve subjects with bipolar disorder during a first manic episode (Salvadore et al., 2010) and decreased by metformin (Barskova et al., 2005; 2009) and anti-epileptic drugs (Krause et al., 1987).

Work in our clinic recently shows that the insulin-mimetic garlic (Sakurai and Adachi, 2005; Patel et al., 2012) significantly enhanced the actions of metformin in reducing alcohol craving and body weight implicating a relationship between mechanisms regulating substance craving and appetite/body weight. This supports previous reports that constituents from garlic such as allicin and diallyl disulphide activate transient receptor potential cation channel, subfamily I, member I (TRPA1) (Emery et al., 2015; Bautista et al., 2005) to decrease body weight and alcohol craving while enhancing cognition most probably by activating glucagon-like peptide-1 (GLP-1) and heme oxygenase-1 (HO-1)/nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (Engel and Jerlhag, 2014; Sarkaki et al., 2012; Ambati, 2013; Shirazi et al., 2013; Zeng et al., 2013). Ferdaoussi et al (2008) have reported that the GLP-1 agonist exendin-4 antagonises interleukin-1 beta that may be associated with diabetes as well as drug addiction (Cearley et al., 2011; Zhang et al., 2015). Additionally, agents such as GLP-1 agonists, garlic, l-cysteine and N-acetyl-cysteine that enhance hydrogen sulphide which inhibits NF-kappa B (Oh et al., 2006; Dai et al., 2013) in tissues may prevent drug reinstatement (Selley et al., 2014; Baker et al., 2003; Peana et al., 2010) especially when combined with metformin which also inhibits NF-kappa β (Isoda et al., 2006) that regulate structural and behavioural plasticity to drugs of abuse such as cocaine (Russo et al., 2009). Additionally, a dysregulated NF-kappa β signalling may be a core characteristic of bipolar disorder (Elhaik and Zandi, 2015), diabetes mellitus (Kiechi et al., 2013); temporal lobe epilepsy (Teocchi et al., 2013) and Alzheimer's disease (Granic et al., 2009).

Lipotoxicity

Lipotoxicity refers to cellular dysfunctions caused by elevated free fatty acid levels playing a central role in the development and progression of obesity related diseases. Saturated fatty acids cause insulin resistance and reduce insulin production in pancreatic cells. The underlying endoplasmic reticulum (ER) stress-response

can lead to beta-cell death (lipoptosis) (Simon-Szabo et al., 2014). Fructose is a cause of insulin resistance and lipotoxicity (Chen et al., 2001; Elliot et al., 2002; Khitan and Kim, 2013). Fructose administration induces the rise of glucose, insulin, total cholesterol, triglyceride, free fatty acids and methylglyoxal (Lu et al., 2013) and may also lead to decreased neurogenesis in the hippocampus (van der Borght et al., 2011). Methylglyoxal is a highly reactive dicarbonyl generated during glucose and fructose metabolism. It is a major precursor of advanced glycation end-products (AGE) and induces activation of the renin-angiotensin system (Dhar et al., 2013). Ten percent fructose administration for three to five weeks induces the metabolic syndrome with over-expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6, transforming growth factor beta-1, plasminogen activator inhibitor-1 (PAI-1) and monocyte chemoattractant protein 1 (Yang et al., 2014; Shalam et al., 2006). From our experience and probably due to species differences, this may not be uniformly replicated in all laboratories. Chronic fructose feeding is reported to lead to lower insulin receptor mRNA with attendant decrease in insulin sensitivity in skeletal muscle and hyperinsulinaemia. There is then not only hypertriglyceridaemia but also hyperuricemia probably due to upregulation of sterol regulatory element binding protein-1c by peroxisome proliferator-activated receptor-gamma-coactivator-1 beta (PGC-1 β) (Nagai et al., 2009). Fructose undergoes phosphorylation by fructokinase to fructose-1-phosphate (using ATP), a reaction that has no negative feed-back mechanisms (Abdulla et al., 2011) unlike glucokinase and phosphofructose. Accumulation of the phosphorylated substrate and depletion of ATP leads to high uric acid levels, a cause of the metabolic syndrome (DeBosch et al., 2014). Mice lacking the enterocyte uric acid transporter, GLUT 9, develop early-onset metabolic syndrome.

Free fatty acids from stored triglycerides or diet-derived chylomicrons increase cardiometabolic risk. Free fatty acids, acyl-CoAs, ceramides, and diacylglycerol increase PKC, c-Jun N-terminal kinase (JUNK) and the inhibitor of IK β α , which is IKK kinase and related kinases. These then impair insulin signalling by increasing the inhibitory serine phosphorylation of insulin receptor substrate (IRS) (Qatanani and Lazar, 2007).

Free Fatty Acids Activate Toll-Like Receptors

In addition, free fatty acids activate Toll-like receptor 4 (TLR 4) (Nguyen et al., 2014); increase endoplasmic reticulum (ER) stress, mitochondrial dysfunction to cause insulin resistance, and decrease peroxisome proliferator-activated receptor gamma-coactivator-1 alpha (PGC 1 α) important for modulation of dopaminergic activity (Ciron et al., 2010). The activities of TLRs are regulated by glycogen synthase kinase (Martin et al., 2005; Wang et

al., 2011) whose non-specific inhibitors such as the cannabinoids (Martin-Moreno et al., 2012) and metformin (Sag et al., 2008) may suppress the production of interleukin- β , interleukin-6, interleukin-12 and tumor necrosis factor whilst enhancing production of interleukin-10. Mice lacking TLR 4 are protected from the ability of lipids to induce insulin resistance. TLR 4 is target gene of CCAAT/enhancer binding protein delta which regulates inflammatory responses (Balamurugan et al., 2012) and modulates obesity-induced inflammation and insulin resistance (Jia et al., 2014) through PKC activation (Loefering and Lennartz, 2011), for example, PKC epsilon which may play a critical role in mediating fat-induced insulin resistance (Samuel et al., 2007). Genetic variations of TLR-4 may be associated to bipolar disorder (Oliveira et al., 2014) and epilepsy (Gan et al., 2013).

Specific alterations in TLR agonist-mediated cytokine release contribute to the evidence of immune dysfunction in bipolar disorders (McKernan et al., 2011) and epilepsy (Maroso et al., 2010). The AMPK activator, metformin, may acutely and chronically suppress TLR 4 signaling (Soraya et al., 2014) which may also be upregulated by morphine released by activated neuroglia during drug addiction (Kovacs, 2012), providing support for a relationship between cardiometabolic and neuropsychiatric disorders.

Bipolar Disorder

Bipolar disorder (BPD), which is associated with the highest suicide rate among all disorders (Malhi et al., 2010), is a severe neuropsychiatric disease. It is characterised by recurrent episodes of mania, pathologically energised states with misguided volition and behaviour. The mood state is of intoxicating euphoria (or irritability) and depressions that are low moods with compromised energy, volitional states and also diminished cognitive capacity (Chen et al., 2014). It affects 1% of the population.

Family and twin studies show bipolar disorder has a strong heritable component (Lohoff et al., 2006). In bipolar disorder I, there is mania and major depression in ratio of 1: 3. Bipolar disorder II has hypomania and major depression in ratio of 1: 40. Bipolar disorder (BPD) III or cyclothymic disorder has hypomania and depression in ratio of 1: 1. Bipolar disorder IV (BPD IV) is mania or hypomania induced by antidepressant therapy. BPD V consists of only major depression and there is a family history of bipolar disorder. Bipolar spectrum disorder includes depression (especially treatment-resistant depression), impulsivity disorder, substance abuse disorder, eating disorders, personality disorders and childhood behavioural disorders.

A link between mood disorders and substance abuse

Nearly 60% of individuals with bipolar disorder have a co-

occurring substance use disorder (Verduin et al., 2005) or drug addiction defined as a chronic, relapsing brain disease that is characterised by compulsive drug seeking and use despite harmful consequences (Volkow, 2014). This implicates a link between mood disorders and substance abuse or dependence disorders and a genetic link between alcoholism and bipolar disorder has been suggested (Brady and Lydiard, 1992; Sonne and Brady, 2002; Merikangas and Gelemtter, 1990; Merikangas et al., 2008). Individuals with manic symptoms may be at greater risk for the later onset of alcohol and cannabis dependence.

Bipolar Disorder is related to Type 2 Diabetes Mellitus

The relationship between bipolar disorder and type 2 diabetes mellitus has been noted to be more than just comorbid disorder (Calkin et al., 2013; McIntyre et al., 2009). Metabolic disturbances in bipolar disorder appears to be a cluster of diseases that demonstrate insulin resistance as their common aetiological factor (Yumuru et al., 2012). There is insulin resistance in bipolar disorder (Gomes et al., 2010); and type 2 diabetes or even pre-diabetes may be risk factors for smaller hippocampal and cortical volumes in bipolar disorder (Hajek et al., 2014). Shared pathophysiology linking the two disorders include hypothalamic-pituitary-adrenal and mitochondrial dysfunctions, inflammation, excitotoxicity, glucocorticoid signalling, common genetic links, and epigenetic interactions which increase cardiometabolic risk with effects on the CNS.

These adaptations and the physiological toll equate to allostatic load (McEwen, 2003; Brietzke et al., 2011) while the significant depressive symptoms in bipolar disorder could be termed 'metabolic syndrome type II' (McIntyre et al., 2007). Patients with bipolar disorder and type 2 diabetes mellitus have more severe course of illness and are more refractory to treatment. Maina et al (2008); Rogenold et al (2002) had observed that there is increased prevalence of type 2 diabetes mellitus and significant correlates of overweight in drug-naïve patients with bipolar disorder. Overall results point to the presence of an association between bipolar disorder and metabolic syndrome as well as between their subcomponents (Czepielewski et al., 2013; Brietzke et al., 2011; McIntyre et al., 2010). In support of this stance is the finding that the elevated insulin-like growth factor-I (IGF-I) in bipolar disorder may be a trait marker for the disease (Kim et al., 2013).

Bipolar disorder is also related to Alzheimer's disease

Several similarities have also been observed between

bipolar disorder (bipolar spectrum disorder) and Alzheimer's disease in terms of clinical presentation, temperament and neurobiology. Both pathologies respond to drugs that decrease cortisol or block glutamate receptors and Alzheimer's disease may be termed bipolar type VI (Akiskal et al., 2014). Brain insulin resistance is an early and common feature of Alzheimer's disease (Talbot et al., 2012) and is associated with IGF-I resistance, insulin receptor substrate-1 (IRS-1) dysregulation and cognitive decline. Alzheimer's disease shows many age-related pathophysiological features of type 2 diabetes mellitus which include insulin resistance, disrupted glucose metabolism in non-neuronal tissues, peripheral oxidative and inflammatory stress, amyloid aggregation, neural atrophy and cognitive decline. Alzheimer's disease may now be termed type 3 diabetes mellitus (de la Monte, 2012; Yanev et al., 2013; Chaldakov et al., 2014). In selected cardiometabolic diseases (type 2 diabetes mellitus, metabolic syndrome, obesity, atherosclerosis) and neuropsychiatric diseases (Alzheimer's disease, Huntington's disease, Parkinson's disease, epilepsy, bipolar spectrum disorder, depression, schizophrenia, primary headache, diabetic retinopathy, rett syndrome), the levels of brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are low (Chaldakov et al., 2014; 2009; Nousen et al., 2013). The neuronal glucose transporter (GLUT 3) and adenosine monophosphate-activated kinase (AMPK) are reduced in Alzheimer's disease (Khatri and Man, 2013). The energy sensor, AMPK, when activated by insulin sensitizers such as metformin + exenatide (Li, 2007) reduces oxidative stress, improves mitochondrial dysfunction, improves glucose uptake in Alzheimer's disease (AD) and slows down the main amyloidogenic protein, A β , accumulation extracellularly and intracellularly or tau hyperphosphorylation intracellularly (Kim et al., 2011). Though metformin alone is recommended not to be used for Alzheimer's disease because it may upregulate BACE1 (beta-secretase) transcription (Chen et al., 2009), Whitmer (2013) has reported that metformin cuts AD-linked dementia rates more than insulin, thiazolidinediones or sulphonylureas. Moreover, the initial report by Chen et al (2009) has also been contradicted by recent investigations by Hettich et al (2014) who showed that the biguanide, metformin, reduces BACE1 enzyme levels making it of value in treating or preventing AD. Metformin decreases neuronal insulin resistance and is associated with neurogenesis (Wang et al., 2012). It also protects against vascular dementia. Metformin, not rosiglitazone, attenuates the increasing plasma levels of the new cardiovascular/ bipolar disorder I marker, fibulin-1 (Skov et al., 2014; Greenwood et al., 2012).

Hyperglycaemia is linked to Epilepsy

The International League Against Epilepsy (ILAE) (Fisher

et al., 2014) classifies epilepsy as a disease of the brain defined by the following conditions, 1) at least two unprovoked (or reflex) seizures occurring > 24 hours apart; 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general occurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years; 3) diagnosis of an epilepsy syndrome. The most common type (60%) of seizures are convulsive (Algreeshah et al., 2013).

People with hyperglycaemia tend to have focal or local seizures (Maccario et al., 1965; Alajbegovic et al., 2002; Moien-Afshari and Tellez-Zenteno, 2009) and seizure may be the first presentation of diabetes mellitus (Omar et al., 2012) where hyperosmolality and dehydration may increase the metabolism of gamma-amino-butyric acid (GABA) and decrease seizure threshold (Ghasemi et al., 2010). Diabetic hyperglycaemia is associated with the severity of epileptic seizures in adults (Huang et al., 2008; Kirchner et al., 2006; Schwechter et al., 2003). While high glucose concentrations are associated with pro-convulsant effects, glucose depletion contributes to an arrest of epileptiform activity in the system of the entorhinal cortex-hippocampus network. Calorie restriction inhibits seizure susceptibility in epileptic mice by reducing blood glucose (Greene et al., 2001).

There is increased expression of Notch 1 in temporal lobe epilepsy (Liu et al., 2014) and diabetes (Li et al., 2013). High-fat diet also reduces brain-derived neurotrophic factor (BDNF)-neuropeptide Y (NPY) signalling (Azoulay et al., 2008; Yoo et al., 2011) important for attenuation of seizures and neuroprotection (Kuromitsu et al., 2001; Loscher et al., 2010; Silva et al., 2007; Urabe et al., 2013).

Additionally, there is accumulating evidence that chronic epilepsy and prolonged use of present anti-epileptic drugs are associated with atherogenesis due to their resultant hypercholesterolaemia, dyslipidaemia, hyperhomocysteinaemia and hyperuricaemia (Hamed and Nabeshima, 2005) which are factors of the metabolic or insulin resistancesyndrome (Alberti et al., 2005). Cases of familial hyperinsulinaemia associated with epilepsy have been described (Idris et al., 2004).

Epilepsy is linked to bipolar disorder and is associated with drug addiction

About 34% of patients with epilepsy have mood disorders (Algreeshah et al., 2013). Bipolar disorder like Alzheimer's disease and type 2 diabetes mellitus may be an age-related disorder where brain structural changes, cognitive deficits, oxidative stress imbalance, A β deposits, immunosenescence, telomere shortening and neurotrophin deficiency are important pathophysiological changes (Rizzo et al., 2014) and metformin is reported to prevent premature senescence associated with age-related illnesses (Oriaifo et al., 2015) and able to correct

the pathophysiologic changes. Animal models support a potential role of pathogenic mechanisms of mood disorders in the development of epileptic seizures and epileptogenesis (Kanner et al., 2014). Depression and manic episodes are described in bipolar disorder and in epilepsy (Kudo et al., 2001; Epps et al., 2012) underlining a bidirectional relationship. Manic attacks in dogs seem to resemble epileptic seizures (Phillips, 2005). Also, epileptic seizures are linked to use of substances of abuse (Alldredge et al., 1989; Personal Communication, 2006).

Epilepsy and Alzheimer's disease

There is accelerated brain ageing in severe chronic epilepsy who may have features resembling Alzheimer's disease (Thorn et al., 2011) with increased prevalence of AD in drug-resistant epilepsy. The insulin sensitizer, metformin (ClinicalTrials.gov Identifier: NCT 01965756; Gupta et al., 2011; Mathieu-Costello et al., 2003), attenuates Alzheimer's disease biomarkers and neuropathology by decreasing activated c-jun-N-terminal kinase, phospho-tau, total tau and attenuating the reduction of synaptophysin in the disease (Li et al., 2012). There is tau protein accumulation in chronic epilepsy (Thorn et al., 2011). Metformin has recently been demonstrated to reduce the main amyloidogenic enzyme, β -secretase (Hettich et al., 2014) and thus inhibit $A\beta$ neurotoxicity.

Signal transduction by neuronal insulin receptors is strikingly sensitive to disruption by soluble $A\beta$ oligomers (Zhao et al., 2008). Inositol stereoisomers, which are upregulated by metformin (Baillargeon et al., 2004), are anti-epileptogenic (Bazan and Musto, 2009), inhibit $A\beta$ neurotoxicity and protect against the synaptic targeting by these oligomers (Pitt et al., 2013) in Alzheimer's disease.

Sleep disorders, insulin resistance, bipolar disorder and epilepsy

Wright (1993) reported a case of mania following sleep deprivation for four nights. Other workers (Tufik et al., 1978; Gessa et al., 1995; Suchecki, 2000; Armani et al., 2012) reported induction of mania in sleep models. Benedetti et al (2008) reported sensitization to repeated sleep deprivation in animal models while Holst et al (2014) reported pronounced hyperactivity in dopamine transporter (DAT) knock-out animals. Poor sleep has been noted (Kamphuis et al., 2011) to be a potential causal factor in aggression and violence. Sleep deprivation, which is associated with impaired glucose homeostasis (Naidoo et al., 2014), facilitates the onset of epileptic seizures (Fountain et al., 1998; Diaz-Negrillo, 2013). High-fat diet increases sleep fragmentation (Kotz et al., 2012) and may decrease brain GABA levels

(Valladolid-Acebes et al., 2011).

All these reports point out that repeated sleep deprivation may upregulate dopaminergic signalling, a causal factor in facets of bipolar disorder and epilepsy; and rapid eye movement (REM) sleep-deprived rats are more responsive to apomorphine (Tufik et al., 1978). Inadequate sleep, which is associated with low BDNF scores (Singh et al., 2014), has recently been recognised also as an important risk factor for insulin resistance and diabetes (Naidoo et al., 2014). The workers pointed out that even relatively short bouts of sleep deprivation reduce glucose tolerance by as much as 40% in aged rodents, though not in the absence of food. Sleep deprivation induces the unfolded protein response (UPR) in the brain, with robust induction of the chaperone protein, binding immunoglobulin protein (BiP) (which is neuroprotective) following marked increase in the pro-apoptotic transcription factor, C/Enhancer binding protein homologous protein (CHOP). The UPR is a coordinated adaptive response to limit the accumulation of unfolded proteins in the endoplasmic reticulum and can be induced by perturbations in calcium signalling, glucose/energy deprivation or excessive secretory protein synthesis. The insulin sensitizer, metformin, causes lower induction/activation of various endoplasmic reticulum-stress markers such as CHOP (Simon-Szabo et al., 2014). Activation of the X-box binding protein-1 (XBPI), which is required for UPR and impaired in bipolar disorder, results in relief of endoplasmic reticulum stress and establishment of euglycaemia (Wang and Kaufman, 2012; Lee et al., 2011; Kakiuchi et al., 2003). Normally, XBPI helps upregulate the chaperone protein, BiP. The UPR is also upregulated in disease-states such as type 2 diabetes mellitus (upregulation of the spliced variant of XBPI (Engin et al., 2014, though its over-activation may result in apoptosis)), Alzheimer's disease and Parkinson's disease (Hoozemans et al., 2012). Reduction in oxidative stress by metformin may be beneficial in diabetes and sleep disorder control (Abdulkadir and Thanoon, 2012).

5'- AMP- Activated kinase regulates circadian clock

Glucose, lipid homeostasis and adiposity are under clock control and mice with aberrant clock function exhibit features of the metabolic syndrome (Rudic, 2009). AMPK activation restores the 24-hour pattern of clock genes, decreasing glucagon levels and increasing leptin levels (Vieira, 2014). Activation of AMPK with metformin induces casein kinase-I dependent degradation of the clock protein, Period 2 (mPer2) (Um et al., 2007). Casein kinase-I epsilon, an essential component of the core molecular clock genes, is a REM sleep candidate gene. It phosphorylates Period (Per) and cryptochrome (CRY) proteins, the negative regulators of the feedback loop of the circadian clock, thus facilitating their degradation and

translocation and consequently regulating the circadian period (Zhou, 2012). Casein kinase-I epsilon is also a negative regulator of psychostimulants such as heroin and opioids (Bryant et al., 2009). Activated casein kinase-2 and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling are reported (Iniaghe et al., 2015) to confer neuroprotection in murine intracerebral haemorrhage, though, casein kinase-I delta and epsilon may not play a major role in the risk of major psychiatric disorders (Matsunaga et al., 2012).

Genetic influence in bipolar disorder, substance abuse, epilepsy and type 2 diabetes mellitus

Genetic and epigenetic influence over neuropsychiatric and cardiometabolic disorders is multifactorial and variable. For example, polymorphisms within the coding regions of the serotonin 5HT_{2A} receptor locus have been found in some studies to be positively associated with neuropsychiatric and cardiometabolic disorders (Nichols, 2009; Sklar et al., 2008). Deficits in 5HT_{2A} receptor function (which includes deficits in anti-TNF- α activity and blood pressure regulation) may underlie part of the co-morbidity of neuropsychiatric and cardiometabolic disorders. Genome-wide expression analysis has also identified chemokine (chemoattractant cytokine) signalling and toll-like receptor signalling as convergent epileptogenic pathways (Sharma, 2012). Kan et al (2012) demonstrated that there is upregulation of genes involved in chemokine signalling in epileptogenesis; and downregulation of multiple GABA system-related genes (Arion et al., 2006).

There is significant association between bipolar disorder and polymorphism in the TNF- α gene (Pae et al., 2004), interleukin-1 cluster group (Papiol et al., 2004; 2008) and variations in the vesicular monoamine transporter 1 (VMAT1) gene (Lohoff et al., 2006). Cyclic adenosine monophosphate response element binding protein 1 (CREB 1) gene polymorphism is associated with cognitive dysfunction, dysfunction in selective attention and retrieval of long-term memory in major depression (BPD V) (Guo et al., 2014). Lithium and valproate, effective pharmacotherapies for bipolar disorder, increase the expression of VMAT1. An expanded convergent functional genomics approach (Ogden et al., 2004) shows the dopamine and cAMP-regulated phosphoprotein of 32 Kda (DARPP-32) tops the list of candidate genes followed by preproenkephalin (PENK) and then tachykinin 1 (substance P). Clock gene D-box binding protein (DBP) is also a candidate gene for bipolar disorder (Le-Niculescu et al., 2008). DBP knock-out mice are activated by sleep disorders and increase alcohol intake following stress, similar to bipolar patients.

Monocytes of bipolar patients exhibit a coherent mutually correlating set (signature) of 19 aberrantly expressed mRNAs of inflammatory, trafficking, survival

and mitogen-activated protein kinase pathway genes when compared with control. Genome-wide association studies strongly suggest that the genetic predisposition to bipolar disorder is due to a combination of many common variants (Brietzke et al., 2011) and that there are overlapping genes in both bipolar disorder and metabolic syndrome. The TSPAN gene which encodes a tetraspanin protein involved in the organisation of cellular receptors and signalling represents a susceptibility locus for both type 2 diabetes and bipolar disorder in genome-wide association studies (Zeggini et al., 2008; Sklar et al., 2008). Also, BDNF val66met polymorphism is associated with both bipolar disorder (BPD) and metabolic syndrome (MS) (Fan and Sklar, 2008). Early life stress may be a mediator of the increased inflammatory activity found in bipolar disorder.

DNA methylation causes gene silencing (Bird et al., 2009). DNA methylation of certain genes has been found to mediate persistent epileptiform activity *in vitro* and *in vivo* (Machnes et al., 2013) and is implicated in drug seeking behaviours (Massart et al., 2015). There may be increased DNA methylation in bipolar disorder at specific BDNF promoters leading to decreased neural BDNF levels which may be a biomarker for the disease (Ikegame et al., 2013). Hypermethylation of BDNF promoter region is specifically found in bipolar disorder II with lithium and valproate showing significant reduction of hypermethylation (D'Addario et al., 2012; Dell'Osso et al., 2014). Also, DNA methylation profiling implicates several genes in type 2 diabetes. Top association was for a cytosine-phosphate-guanine (CpG) site in the TXNIP gene (Carless et al., 2013); known to modulate glucose metabolism and insulin sensitivity. It likely plays a role in type 2 diabetes and contributing to the therapeutic action of metformin. In the same vein, obesity caused by high-fat diet increases DNA methylation at the leptin promoter in rat adipocytes (Kalliman and Parrizas, 2011). Prenatal poor nutrition or high-fat diet, exposure to tobacco smoke or ethanol, glucocorticoids and methyl donors may influence adult lipid metabolism by DNA methylation (Napoli et al., 2011; Yajnik, 2010). The expression of endothelial nitric oxide synthase (eNOS) is influenced by DNA methylation (Chan et al., 2004) and aberrant methylation of the asymmetric dimethylarginine degrading enzyme dimethylarginine dimethylaminohydrolase (DDAH) induced by homocysteine (Zhang et al., 2007). Sufficient level of hydrogen sulphide is able to inhibit mitochondrial transcription factor A (TFAM) promoter methylation and maintain mitochondrial DNA copy number (Li and Yang, 2015). Moreover, class I HDAC inhibition blocks cocaine-induced plasticity through targeted changes in histone methylation (Kennedy et al., 2013) and opposes the effects of sirtuin 1 (HDAC 3) (Renthal et al., 2009).

Upregulation of the non-coding microRNAs 29b and microRNA 132 and downregulation microRNAs 134 and 34a may be beneficial in cardiometabolic and

neuropsychiatric disorders (Zhu et al., 2013; Zheng et al., 2013; Hu et al., 2012; Jimenez-Mateo et al., 2012; Zhou et al., 2009; Rong et al., 2011). Cocaine decreases microRNA-124 and upregulates microRNA-212 and CREB-microRNA-212-X-linked transcriptional repressor methyl CpG binding protein 2 (MeCP2)-BDNF signalling is responsible for cocaine tolerance and escalating intake (Robison and Nestler, 2007; Im et al., 2010). Striatal MeCP2 signaling is pro-addictive.

Impaired feedback regulation of XBPI transcription factor may be a genetic risk factor for bipolar disorder (Kakiuchi et al., 2003). XBPI, upregulated by valproate (Kim et al., 2009) and by metformin (Kim et al., 2014), is neuroprotective and prevents the accumulation of free calcium (Ca^{2+}) in the cytosol, a process that down-regulates amyloid-beta neurotoxicity (Casas-Tinto et al., 2011). Also, Glu 640 Arg single nucleotide polymorphism of ATP P2X7 receptor is a potential susceptibility gene for bipolar disorder and major depression (Skaper et al., 2009).

Biomarkers for Bipolar Disorder and Epilepsy

Protein biomarkers for depression by multi analyte profiling of case-control collections (Domenici et al., 2010) show insulin as topping the list, followed by matrix metallo-proteinase-9 (MMPs), alpha-2 macroglobulin and tissue inhibitors of metallo-proteinase (TIMP). Insulin tops the list probably because metabolic syndrome is associated with bipolar disorder in 31% of cases (Vuksan-Cusa et al., 2010). Central insulin signalling may increase the surface expression of the GABA_A receptor, facilitating neuroprotection (Mielke et al., 2006) and anti-epileptogenesis. MMP-9 has a key role in the CNS though its overexpression may be epileptogenic (Yin et al., 2011) and polymorphism in the MMP-9 gene as well as inflammation may be a mediating factor amongst cardiovascular disorders, cancer, bipolar disorders and epilepsy (Rybakowski, 2009; Rybakowski et al., 2013; Yin et al., 2011; Kim et al., 2013; Vezzani and Friedman, 2014; Wilczynski et al., 2008). This may explain the comorbidity between some somatic and neuropsychiatric illnesses. MMP-9 is able to process several proteins crucial for synaptogenesis, synaptic plasticity and long-term potentiation. MMP-9 is able to modulate cytokines and growth factors such as tumor necrosis factor-alpha and BDNF by processing the pro-forms into the active proteins. TIMP binds to MMP-9 and regulates its activity, able to prevent MMP-9-dependent late long-term potentiation important for epileptogenesis.

Biological markers help in prevention and early intervention at the prodromal stage of affective disorders. C-reactive protein may be a biomarker of de-novo depression risk in bipolar disorder (Walker et al., 2014) and also of metabolic syndrome (Vuksan-Cusa et al., 2010). Other biomarkers are tumor necrosis factor-alpha,

interleukin-6 and interleukin-10. Increases in interferon-gamma (IFN-gamma) are associated with dysregulation of the tryptophan metabolite pathway via 2, 3-dioxygenase activation. BDNF and glycogen synthase kinase are also useful biomarkers. Individuals who exhibit allele-specific DNA demethylation in functional glucocorticoid response element of FK506 binding protein 5 (FKBP5) are prone to developing persistent cortisol dysregulation. This association is found to be associated with trauma in early life (Walker et al 2014). Others include alterations in markers for lipid peroxidation, for example, 8-isoprostaglandin F (2 alpha), oxidative damage to DNA (8-hydroxy-2-deoxyguanosine) and RNA (8-hydroxyguanosine).

Defective mitochondrial biogenesis is a hall-mark of the metabolic or insulin resistance syndrome, Drug Addiction, Epilepsy and neurodegenerative diseases

Metformin, glucagon-like peptide-I (GLP-I), cannabinoid CB2 agonists, artemisinin, carvedilol and valproate are drugs that increase eNOS to upregulate mitochondrial biogenesis (Figure 1) and activate anti-oxidant systems which may be anti-diabetogenic and antiepileptogenic. Mitochondrial dysfunction as a result of defective endothelial nitric oxide signalling (Sartori and Scherrer, 1999) is a hall-mark of the high cardiovascular risk in the metabolic syndrome (Nisoli et al., 2007; 2005; 2003; Patel et al., 2000; Jobgen et al., 2006; Joseph et al., 2012); epilepsy (Waldbaum and Patel, 2010; Martinc et al., 2012); drug addiction (Dietrich et al., 2005; Chudy et al., 2014; Cunha-Oliveira et al., 2013) where there is decrease in mitochondrial DNA copy number (Feng et al., 2013; Lee et al., 2009); Alzheimer's disease (Moreira et al., 2010; Aulston et al., 2013); decreased threshold to MPTP - induced seizures (Chen et al., 2011) and bipolar disorder (Young, 2007; Kato, 2007; Kato and Kato, 2000).

Role of endothelial nitric oxide in mitochondrial function

Endothelial nitric oxide through boosting anti-oxidant mechanisms and decreasing brain excitability may occupy a central place in cardiometabolic and neuropsychiatric disorders (Chen et al., 2013; Patel et al., 2000; Murashima et al., 2000; Ferraro and Sardo, 2004; Wang et al., 2014, 2015; Oriaifo et al., 2015). It decreases lipid peroxidation while upregulating glutathione production and serotonin release. Endothelial nitric oxide signalling to PGC-I alpha (Figure 1) *vis-a-vis* reactive oxygen species/ matrix-metalloproteinases /glycogen synthase kinase-3 β may have opposing roles in the aetiopathogenesis of excitotoxicity, pancreatic beta-cell exhaustion and neurodegeneration (Dietrich et

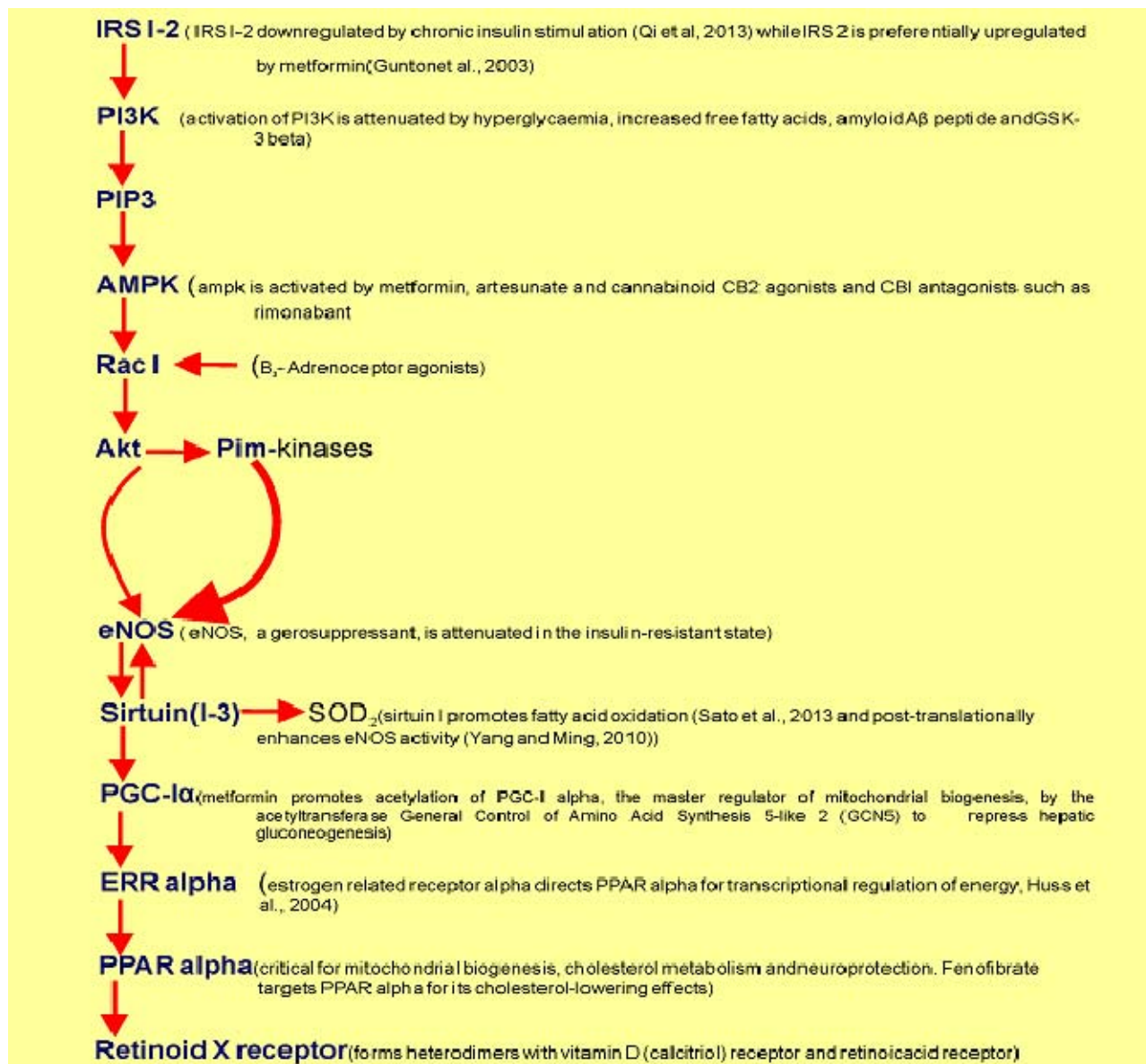


Figure1: Metformin, GLP-1 artesunate and cannabinoid CB2 receptor agonists upregulate Akt-eNOS signaling to PPAR alpha to enhance mitochondrial biogenesis and lipid oxidation

Figure1: Metformin, GLP-1, artesunate and cannabinoids increase PPAR alpha signaling important for mitochondrial function and lipid oxidation, thereby attenuating the effect of ROS/MMPs/GSK-3 beta signaling which poses risk for atherosclerosis, coronary artery disease, stroke and seizure susceptibility. GLP-1: glucagon-like peptide; IRS: insulin receptor substrate; P13K: phosphoinositide 3-kinase; PIP3: phosphatidylinositol 3,4,5-triphosphate; AMPK: 5' adenosine monophosphate activated protein kinase; Rac1; GTPase; AKT: protein kinase: pro-viral insertion site for moloney leukaemia virus; Enos: endothelial nitric oxide synthase; Sirtuin I; NAD-dependent deacetylase silent information regulator; PGC-1 alpha: peroxisome proliferator activated receptor gamma- coactivator I alpha; ERR alpha: estrogen related receptor alpha; PPAR alpha: peroxisome proliferator activated

al., 2005; Ceriello et al., 2004; Hink et al., 2001; O'Sullivan et al., 2014; Cerqueira et al., 2011). While metformin upregulated endothelial nitric oxide synthase (eNOS) mRNA (Kim et al., 2007), methamphetamine had no effect on eNOS mRNA (Friend et al., 2013) which may be at the basis of methamphetamine-induced

neurotoxicity. There is deregulation of ceramide production in mitochondrial dysfunction (Novgorodov and Gudz, 2011) and inhibition of sphingomyelinases represent a novel action of nitric oxide (Barsacchi et al., 2007) which might be relevant in anti-apoptosis (Stafstrom, 2003), insulin resistance (Hansen et al.,

2014), status epilepticus (Mikati et al., 2003; Schauwecke, 2012) and bipolar disorder (Schwarz et al., 2008).

Garlic may potentiate the effects of metformin

Increased hydrogen sulphide consumption by hyperglycaemic cells may lead to dampening of Akt-mediated cardioprotection (Szabo, 2012; King et al., 2014). While increased generation of hydrogen sulphide (H₂S) by garlic and metformin may enhance mitochondrial function and rescue eNOS from peroxynitrite-induced uncoupling (Benavides et al., 2013; Wilinski et al., 2013; Guo et al., 2012; Gu et al., 2012). Garlic and metformin may help prevent AD (Wang et al., 2011) and depression (Chen et al., 2013) partly through H₂S which upregulates nitric oxide production (Wilinski et al., 2011). Studies (Kamat et al., 2015; 2013) have shown that hydrogen sulphide attenuates homocysteine-induced mitochondrial toxicity and neurodegeneration mediated through NMDA receptors, implicating a possible preventive action of metformin and garlic.

AMPK Activators Enhance Mitochondrial Function

Metformin, adenosine, adiponectin, ghrelin, adenine nucleotides, valproate, artesunate and cannabinoid CB2 receptor agonists/CB1 inverse agonists activate AMPK (Graham Hardie: www.lifesci.dundee.ac.uk; Towler and Hardie, 2007) and increase proteins involved in enhancing mitochondrial function (Figure 1). These proteins exhibit a redox control of MMPs (Nelson and Melendez, 2004) and limiting ROS accumulation and the inflammatory state (Wang et al., 2015; Besse-Patin and Estall, 2014; Sitarc et al., 2014; Tedesco et al., 2008). A normally functioning mitochondrion helps to attenuate the effects of nutrient overload and hyperglycaemia (Aulston et al., 2013) on negatively impacting on insulin receptor substrate signalling to phosphatidylinositol 3, 4, 5-triphosphate (PIP3) (Figure 1).

Metformin increases extracellular ATP levels (Piwkowska et al., 2013) which may inhibit GSK-3 beta (Sutherland et al., 1993) and allosterically potentiates GABA_AR-gated chloride channels to regulate neuronal excitability (Liu and Wang, 2014). A major effect of extracellular ATP is attenuation of recurrent epileptiform discharges through adenosine receptor A1 activation (Klaft et al., 2012) and the endothelial nitric oxide upregulation. The (ATP) P2X7 receptor-pannexin 1 complex decreases seizure susceptibility (Kim and Kang, 2011).

Metformin, cannabinoid CB2 agonists, valproate upregulate genes important for mitochondrial biogenesis (such as the PGC-1 alpha gene) including genes for lipid oxidation, glycolysis and stress response (Oriaifo, 2001; Martin-Montalvo et al., 2013, Tedesco et al., 2008, 2010;

Sitarc et al., 2014; Cowell et al., 2009; Zheng et al., 2013). The transcriptional co-activator, PGC-1 alpha, is a recognised master regulator of mitochondrial biogenesis and oxidative metabolism (Handschin and Mootha, 2005); and metformin and cannabinoid CB2 agonists may in concert increase its interaction with estrogen-related receptor-alpha (ERR α) (Huss et al., 2004; Priestley et al., 2015; Sun et al., 2007) to direct PPAR alpha for transcriptional regulation of energy. PGC-1 alpha gene polymorphism may be associated with alcohol consumption (Frances et al., 2008) and its expression decreases in Alzheimer's disease (Qin et al., 2009). The PGC-1 alpha 4 (PGC-1 α 4)-regulated hormone, meteorin-like, promotes browning of white adipose tissue by inducing interleukin 4/13 and activating M2 macrophages (Rao et al., 2014; Qiu et al., 2014).

PPAR alpha agonists attenuate epileptogenesis, major depression, Alzheimer's disease and drug addiction

Metformin via PPAR-alpha-dependent but AMPK-independent mechanisms upregulate the GLP-1 receptor axis (Maida et al., 2011) and PPAR alpha agonists such as the cannabinoids have been reported to suppress nicotine reward effects and relapse (Mascia et al., 2012) and Alzheimer's disease (Tremblay-Mercier, 2012). The ketogenic diet and fenofibrate are reported to exert anticonvulsive effects via PPAR-alpha (Porta et al., 2008). PPAR agonists attenuate hyperdopaminergic signalling maintained by cholinergic nicotinic receptors in the ventral tegmental area (VTA) (Melis et al., 2011; 2013), and increase adiponectin levels critically useful against major depression (Tsuchida et al., 2005; Leo et al; 2006; Liu et al., 2012).

Metformin, GLP-1, artesunate, valproate and cannabinoid CB2 receptor agonists/CB1 inverse agonists upregulate AMPK activation

The serine/threonine kinase, 5'-adenosine monophosphate activated protein kinase (AMPK), the key energy sensor with the ability to metabolically adapt to external cues, is activated upon an increase in AMP/ATP ratio. AMPK acts as an important mediator of the beneficial effects of calorie restriction and metformin (Towler and Hardie, 2007), GLP-1 agonists (Ben-Shlomo et al., 2011), artesunate (Wang et al., 2015; Tan et al., 2014), valproate (Avery and Bumpus, 2013) and cannabinoid CB2 agonists (Tedesco et al., 2010). AMPK exerts dual regulatory effects on the PI3K pathway, enhancing PIP3-Akt-eNOS signalling while inhibiting mTOR/S6K signalling which has negative effect on insulin signalling (Tao et al., 2010). Rimonabant, an antagonist and inverse agonist of cannabinoid CB1 receptors, enhances mitochondrial biogenesis (Tedesco et al., 2008).

Type 2 diabetes mellitus, drug addiction, bipolar disorder and epilepsy underpinnings: mTOR and role of ampk activators

Epidemiological data demonstrate that primary psychiatric disorders are more frequent in people who develop epilepsy before the onset of the seizure disorder than among controls (Kanner et al., 2014). This may support the notion that there may be neurological underpinnings of metabolic syndrome, drug addiction, bipolar disorder and epilepsy (Amann and Grunze, 2005; Kenny, 2011). Common mechanisms at the level of ion channels might include the anti-kindling and the calcium-antagonist and potassium outward current modulating properties of antiepileptic drugs (Mazza et al., 2007; Ghasemi et al., 2010) and AMPK activators such as valproate and metformin (Kim et al., 2013; Zhao et al., 2014). This report by Zhao et al (2014) supports the preliminary observation in our laboratory that chronic administrations of metformin (200 mg/kg daily) and artesunate are protective against pentylenetetrazole-induced seizures. Seizure threshold in diabetic mice is lower than in control mice (Ghasemi et al., 2010). The gerosuppressants metformin, calorie restriction and GLP-1 agonists (via hydrogen sulphide (Selley et al., 2014)) might suppress hyperactive and aberrant mTOR signalling (Shaw, 2009; Potter et al., 2010, O'Callaghan and Roopra, 2014; Dogan et al., 2011; Lee et al., 2012) responsible for the epileptogenic late-long term potentiation (L-LTP), which plays a role in progression of seizures to intractable epilepsy, via reduction in ROS production. mTOR partly mediates insulin resistance (Xin-Long et al., 2011), upregulates proteins such as AMPARs responsible for drug addiction/relapse (Dayas et al., 2012; Neasta et al., 2010) and is a biomarker and central pathway to disorders such as obesity, epilepsy and aging (Perl, 2015). AMPK activators via attenuating microglial activation (Matsushita et al., 2013) and other inhibitors of Mtor such as l-cysteine (Lee et al., 2012) may prevent drug tolerance and reinstatement. The AMPK pathway which is activated by metformin, cannabinoids and valproate may also protect the brain from seizure-induced cell death by upregulating the Bcl₂-modifying factor (Bmf) which prevents neuronal death in status epilepticus (Moran et al., 2013).

Metformin, GLP-1 agonists and the other AMPK activators such as valproate, valsartan and the cannabinoid CB2 agonists may also downregulate Toll-like receptors and the High-Mobility Group Box-1 protein (HMGB1) (Kovacs, 2012; Ha et al., 2014; Avery and Bumpus, 2013; Maroso et al., 2010; Gan et al., 2013); antagonise the cytokine, interleukin-1 (Maroso et al., 2011; Vezzani et al., 2011; Roger et al., 2010; Suh et al., 2010); decrease advanced glycation end-products which is also associated with epilepsy, diabetes and drugs of abuse (Iori et al., 2013; Treweek et al., 2009) and upregulate BDNF (Whitfield et al., 2011; Hashimoto et al., 2002;

Bovolenta et al., 2010) needed for attenuation of seizure progression and effects of microglia activation in diabetes and reward-related neuronal circuits. Additionally, via an AMPK-dependent mechanism, they may suppress matrix metalloproteinase-9 (MMP-9) which is upregulated in epilepsy (Wilczynski et al., 2008; Morizane et al., 2011; Esfahanian et al., 2012; Yin et al., 2011; Wang et al., 2011) and type 2 diabetes mellitus (Das and Maiti, 2013) and may be a potential new target in epilepsy treatment. It is known that metformin indirectly downregulates GSK-3 beta (Neary and Kang, 2006; Ortega et al., 2010) crucial for mossy fibre sprouting in epileptogenesis (Lee et al., 2012) and also involved in bipolar disorder, diabetes and drug addiction. Via AMPK-independent mechanisms in upregulating adenosine signalling and PPAR-alpha, metformin is also in good stead to attenuate epileptiform discharges similar to the ketogenic diet (Maida et al., 2011; Todora et al., 2000; Masino et al., 2009; Masino and Geiger, 2009; Diaz-Negrillo, 2013; Roopra A: www.sciencedaily.com/2008) and calorie restriction (Greene et al., 2001). The ketogenic diet as already mentioned may also be helpful for treatment of bipolar disorder II (Phelps et al., 2013) underlining a relationship between epilepsy and bipolar disorder. Importantly, metformin corrects the circadian desynchrony caused by a high-fat diet (Vieira, 2014; Lee and Kim, 2013).

Inflammatory cytokines are elevated in obesity, type 2 diabetes mellitus, epilepsy, drug addiction and bipolar disorder

Inflammation contributes to the pathogenesis of blood-brain-barrier (BBB) dysfunction and pharmacoresistant epilepsy (Kim et al., 2012; Takata et al., 2013) and is also important in the aetiopathogenesis of drug addiction, type 2 diabetes mellitus and bipolar disorder. Cocaine, alcohol and other drugs of abuse activate NF-kappa β (Kenny, 2011) which maintains cocaine reward (Russo et al., 2009). They also may affect the inhibitory neurotransmission mediated by G-protein gated inwardly rectifying potassium channel (GIRK) (de Velasco et al., 2015) important in bipolar disorder (Farhy-Tselnicker, 2014) and epileptogenesis (Mazarati et al., 2006). Activity of mTORC1 is induced by low levels of ROS, as is the case in cocaine addiction (Dietrich et al., 2005), while mild and high levels may inhibit its activity (Li et al., 2010). Activation of microglia by drugs of addiction, which can be dampened by AMPK activators such as metformin, results in a pro-inflammatory dominance of the innate immune system which is then critically synergised on the neurocircuits of reward and dependence (Kovacs, 2012; Matsushita et al., 2013). These activated microglia elaborate TLR-4 and IL-1 beta during the addictive process. Thus, interleukin-1 receptor/toll-like receptor signalling is critically important in the metabolic

syndrome, bipolar disorder, epilepsy, drug addiction and neurodegeneration. Upregulation of TLR4/NF-kappaB signalling is associated with fetal programming of babies born to obese mothers (Yan et al., 2009; Tong et al., 2009). The endogenous injury sensor, human mobility group box-1 (HMGB1), a trigger of inflammatory cascades is implicated in epileptogenesis (Engel, 2011) and seizure- or epileptogenic injury-induced toll-like receptor 4 (TLR4)/HMGB1 interactions. These interactions activate nuclear factor-kappa β to release pro-inflammatory cytokines also involved, for example, in iktogenesis and can be targeted to reduce seizures (Kim et al., 2012; Maroso et al., 2010; Gan et al., 2013).

C-reactive protein, tumor necrosis factor-alpha, interleukin-6 levels are elevated in type 2 diabetes, epilepsy and bipolar disorder (Brietzke et al., 2011; Maroso et al., 2010). Prolonged activation of cytokines may lead to diminished neurotrophic support, decreased neurogenesis, increased glutamatergic activation (Najjar et al., 2013; Vezzani et al., 2011; Kovacs, 2012), oxidative stress, induction of apoptosis in astrocytes and oligodendrocytes. Tumor necrosis factor- α - nuclear factor-kappa β signalling may be deleterious and may be important in causation of both bipolar disorder and type 2 diabetes mellitus (Moller, 2000; Shulman, 2000; Barrientos et al., 2003; Tilleux and Hermans, 2007; Prossin et al., 2013). Tumor necrosis factor-alpha, the receptors of which are upregulated in major depressive disorder downregulates BDNF (Brietzke et al., 2011) and may increase dopaminergic activity important for manic phase of bipolar disorder (De Laurentis et al., 2002). Interleukin- β which is upregulated by cocaine (Winick-Ng et al., 2012) is capable of inducing cyclooxygenase-2 gene expression and prostaglandin E2 synthesis in islet β -cells (Tran et al., 1999). Prostaglandin E2 is a known inhibitor of glucose-induced insulin secretion.

Cytokine signaling important in aetiopathogenesis of epilepsy, bipolar disorder, type 2 diabetes mellitus and exaggerated dopaminergic signaling is attenuated by metformin and ampk activators

Metformin attenuates the cytokine expression of pro-inflammatory and adhesion molecule genes by upregulating the anti-oxidant heat-shock protein-32 or heme oxygenase-1 (HO-1) (Liu et al., 2011) and inhibiting NF-kappa β via AMPK activation (Hattori et al., 2006). The induction of HO-1 expression mediates the antioxidant and anti-apoptotic effect of AMPK (Liu et al., 2011). Induction of HO-1, which is upregulated by activation of PI3K/Akt/GSK-3 signaling, in brain is important for neuroprotection and neuroplasticity (Kitagishi et al., 2012). Elevated levels of TNF-alpha, which induces NF-kappa B (Theiss et al., 2009), may induce insulin resistance (Moller, 2001), bipolar disorder (Tilleux and Herman,

2007) and epilepsy (Vezzani et al., 2011) via increases in excitatory synaptic strength and decreases in inhibitory synaptic strength (Stellwagen et al., 2005). Protein-tyrosine phosphatase (PTP I β) acts like a physiological negative regulator of insulin signalling and is upregulated by TNF- α (Lorenzo et al., 2008). Furthermore, adipose tissue secretes adipokines, such as TNF- α and leptin, which can downregulate peroxisome proliferator-activated receptor gamma-coactivator-1- α (PGC-1 α), the inducible transcription co-activator important for mitochondrial biogenesis, anti-epileptogenesis and fatty acid oxidation.

TNF-alpha and interleukin- β upregulate SERT (Nichols, 2009; Zhu et al., 2006), decrease BDNF levels (Brietzke et al., 2011) and may increase dopaminergic activity important for epileptogenesis (Stellwagen et al., 2005) and manic phase of bipolar disorder (De Laurentis et al., 2002). Metformin dose-dependently inhibits TNF-alpha and interleukin-1 beta-induced NF-kappa β reporter gene expression (Hattori et al., 2006); while allicin from garlic may decrease interleukin-1 beta mRNA levels (Lang et al., 2004). Interleukin-1 beta is important in the mechanisms of type 2 DM (Dinarelo et al., 2010), epilepsy (Vezzani and Baram, 2007), bipolar disorder (Papiol et al., 2008; Soderlund et al., 2011) and substance addiction (Cearley et al., 2011; Zhang et al., 2015) and may be targeted as a common front for prevention. Chronic metformin may decrease prostaglandin E2 (PGE2) receptor signalling, thereby decreasing steroidogenesis (Xu et al., 2014) as well as decreasing hyperdopaminergic signalling (Kitaoka et al., 2007) via arachidonic acid (Piomelli et al., 1991). Pathological behaviours, such as epilepsy, hypersexuality, hyperlocomotion and aggression, may be mediated by dopamine D3/2 receptors (Kelly et al., 2012), signalling through GSK-3 beta (Li and Gao, 2011). C-reactive protein levels, which are elevated in pilocarpine-induced status epilepticus (Holtman et al., 2013), and may be a biomarker of de-novo depression risk in bipolar disorder (Walker et al., 2014), is lowered by metformin (Oriaifo et al., 2014) which also decreases COX₂ levels (Luchetti et al., 2008) that may be upregulated by NF-kappa B (Crofford et al., 1997) and important for epileptogenesis (Loscher et al., 2010). Metformin and other AMPK activators such as valproate may acutely and chronically suppress TLR 4 signaling (Soraya et al., 2014) and high-mobility group box-1 (HMGB1) (Tsoyi et al., 2011) important for genesis of pro-inflammatory cascades, insulin resistance, bipolar disorder and epileptogenesis showing a convergence of mechanisms amongst these disorders.

Oxidative stress in bipolar disorder, drug addiction, epilepsy and type 2 diabetes mellitus

Oxidative stress also represents an overlapping factor

relevant to the pathogenesis of bipolar disorder, insulin resistance and drug addiction (Kemp and Fan, 2012; McIntyre et al., 2009; Najjar et al., 2013; Dietrich et al., 2005). Oxidative stress and cocaine administration generate reactive oxygen species (ROS) that can activate Jun kinase, p38 mitogen activated protein kinase and increase I kappa β kinase (IKK) to induce insulin resistance (Qatanani and Lazar, 2007), modulate dopaminergic signalling and alter mitochondria and nuclear gene expression (Chudy et al., 2014). IKK specifically phosphorylates the protein that inhibits NF-kappa β , IKK α , resulting in its dissociation from NF-kappa β and, thereby allowing NF-kappa β to migrate to the nucleus to generate the transcription of pro-inflammatory and adhesion molecules. Cocaine, GSK-3 β , oxidative stress and high glucose may activate NF-kappa β to induce matrix metalloproteinase-9 (Kenny, 2011; Zhong and Kowluru, 2013; Zhong et al., 2014) which is pro-apoptotic and may increase sensitivity to pentylentetrazole-induced seizures (Wilczynski et al., 2008). Metformin attenuates the cytokine expression of pro-inflammatory and adhesion molecule genes by inhibiting NF-kappa β via AMPK activation (Hattori et al., 2006). Reactive oxygen species may damage DNA and pancreatic β -cells (Robertson et al., 2004). Tumor necrosis factor-alpha stimulates N-methyl-D-aspartate (NMDA) receptor activity in mouse cortical neurons resulting in early signal regulated kinase (ERK)-dependent death (Jara et al., 2006) and could also induce prostaglandin E2 and glutamate release through TNF- α -COX2 dependent mechanism (Weaver-Mikaere et al., 2013). Interleukin-1 β and interleukin-6 may cause NMDA-dependent neurodegeneration (Viviani et al., 2003; Orellana et al., 2005) and NMDA receptor antagonists and NOS inhibitors may be useful for opioid tolerance and withdrawal (Herman et al., 1996).

Bipolar disorder, Type 2 Diabetes Mellitus, drug addiction and Adipokines

Low levels of BDNF and NGF, also recognised as adipokines, are found in mood disorders, epilepsy, obesity, drug addiction and type 2 diabetes mellitus (Whitefield et al., 2011; McGinty et al., 2010; Singh et al., 2014; Chaldakov et al., 2014; Yanev et al., 2013). Polyunsaturated fatty acids, levels of which may be low in the metabolic syndrome, such as docosahexaenoic and exogenous unesterified arachidonic acid are now known to regulate adult hippocampal neurogenesis via G-protein coupled receptor-40 (GPCR40). Brain – type fatty acid binding protein (FABP7) binds particularly docosahexaenoic acid involved in adult neurogenesis (Tonchev, 2007). High-fat diet reduces brain docosahexaenoic acid, BDNF, CREB, p-synapsin, neuropeptide Y and calcium-calmodulin dependent protein kinase II (CaMKII) (Sharma et al., 2014).

Adiponectin levels are low in mood disorders patients and increases risk for type 2 diabetes mellitus (Taylor and MacQueen, 2010) with high resistin, leptin (leptin resistance) and cortisol (Yumuru et al., 2012; Zeman et al., 2009). Resistin, which inactivates glucose transporter 4 (GLUT 4), and interleukin-6 impairs insulin signalling by down-regulation of insulin receptor substrate (IRS) and upregulation of the suppressor of cytokine signalling, (SOCS-3) which is a negative regulator of insulin signalling (Qatanani and Lazar, 2007). Mice lacking resistin have improved glucose homeostasis. Retinol-binding protein 4 (RBP 4), which also increases insulin resistance, is produced by adipose tissue.

Dysregulated HPA Axis in Bipolar Disorder, Substance Use Disorder and Type 2 Diabetes Mellitus

There is elevated cortisol or glucocorticoid resistance in obesity, type 2 diabetes mellitus and mood disorders due to dysregulation of the hypothalamic-pituitary-adrenal axis (Qi and Rodrigues, 2007; Taylor and MacQueen, 2010; Zeman et al., 2009); with abnormal dexamethasone suppression tests (Rush et al., 1996). The biguanide, metformin, reduces the expression of corticotropin-releasing hormone (Dafopoulos et al., 2013) which plays a key role in the neurobiology of addiction (Zorilla et al., 2014). CRF is genetically upregulated in alcohol-preferring rats (Zhou et al., 2013) and its antagonist CP 154,526 may be effective against cocaine craving (Przgalinski et al., 2005). Stress causes activation of the hypothalamic-pituitary-adrenal (HPA) axis with corresponding increase in cortisol secretion and stimulates CRH synthesis via activation of NF-kappaB (Thomson, 2013) and at excessive concentrations, cortisol can suppress BDNF production (Nessler et al., 2002; Klimpton, 2012; Issa et al., 2010). Acute cortisol treatment increase systemic glycerol and non-esterified fatty acid in plasma while chronically promoting net central fat deposition (Samra et al., 1998). In fact, both metabolic syndrome and major depression (hypercortisolaemic depression) as seen in bipolar disorder share a specific endocrine syndrome that promotes insulin resistance and the accumulation of visceral fat, a marker of increased cardiovascular morbidity and mortality (Weber-Hammer et al., 2002).

Cortisol is also produced by adipose tissue. Adipose tissue contains 11 β -hydroxysteroid dehydrogenase I (11 β -HSD I) which converts the inactive metabolite, cortisone, to cortisol which is known to oppose the anti-gluconeogenic effects of insulin (Qatanani and Lazar, 2007; Wang, 2005) and may induce hypertension through mineralocorticoid receptor activation.

Foetal growth restriction may be associated with increased risk of adult cardiometabolic and neuropsychiatric disorders. Maternal malnutrition (low-protein diet and stress/glucocorticoid exposure may

cause persisting abnormalities (programming) in adult offsprings. Low amino acids, intrauterine growth restriction cause deficiency of placental 11- β -hydroxysteroid dehydrogenase 2 which inactivates cortisol and decreases mineralocorticoid receptor activation and may lead to fetal programming and increased risk of neuropsychiatric disorders (Cottrell et al., 2012; O'Donnell et al., 2011; Shang et al., 2012; Holmes et al., 2015) through NF-kappaB (Tong et al., 2009).

The brain arachidonic acid cascade in bipolar disorder, drug relapse and type 2 diabetes mellitus

Hyperdopaminergic signalling (via upregulation of GSK-3 (Li et al., 2009)) and an upregulated brain arachidonic acid cascade may contribute to bipolar disorder (Ramadan et al., 2011; Bazinet, 2009) as well as to food and drug addiction (Zhuang et al., 2001; Baik, 2013). The endocannabinoid-arachidonic acid pathway may be an important part in the neural machinery underlying relapse which is the resumption of drug taking following a period of abstinence (Yamamoto et al., 2005). Lithium and valproate attenuated brain dopaminergic D2, D3 and D4 receptor signalling involving arachidonic acid when given chronically (Ramadan et al., 2011). Chronic lithium and valproate decrease arachidonic acid turn-over and downregulate brain cyclooxygenase 2 (COX 2) and prostaglandin E 2, thereby decreasing the phospholipase A2- arachidonic acid dependent metabolites and reducing excitotoxicity / neuro-inflammation-induced upregulation of the markers (Kim et al., 2011; Bosetti et al., 2002). Antidepressants upregulate enzymes of the arachidonic acid cascade to different extents thereby causing manic switches, for example, imipramine and fluoxetine (Bazinet, 2009). Also, the products of COX2 and lipoxygenase (LOX) have been implicated in cytokine-mediated damage to β -cells (Persaud et al., 2007) but the secretion of insulin through arachidonic acid does not require its metabolism through COX2 and 5-/12- LOX pathways. Selective inhibitors of COX2 and LOX would have a dual protective role in diabetes – a) minimise β -cell dysfunction, while b) maintain insulin secretion through enhancing endogenous arachidonic acid levels (Persaud et al., 2007). The cyclooxygenase inhibitor, diclofenac, is also useful as anti-relapse measure (Anggadiredja et al., 2004). These results may explain why the combination of metformin and non-steroidal anti-inflammatory drugs is more effective than metformin alone on NGF and BDNF production (Hristova, 2011) while metformin also downregulates the steroidogenic acute regulatory protein (STAR) mRNA expression stimulated by prostaglandin E2 (Xu et al., 2014). Inhibitors of COX2 activity such as metformin may significantly decrease PGE2 production.

There is participation of prostaglandin E2 in dopamine D2 receptor-dependent potentiation of arachidonic acid release (Di Marzo and Piomelli, 1992) and this may be a basis for D1 D2 receptor synergism (Piomelli et al., 1991). Results suggest that prostaglandin E2 is formed in response to dopamine receptor stimulation in the striatum and amplifies both D1 and D2 receptor signalling via prostaglandin receptor EP1. EP1-deficient mice exhibit significant suppression of hyperlocomotion induced by cocaine. Prostaglandin EP1 agonists may augment dopaminergic activity only in the striatum, thus possibly circumventing psychotic symptoms associated with the use of levodopa (Kitaoka et al., 2007).

Immune Activation in Bipolar Disorder and Metabolic Syndrome

The monocyte-T-cell theory of mood disorders considers activation of the immune response system as the driving force behind mood disorders. IL-4, IL-1 beta, TNF-alpha may be strongly associated with bipolar disorder (Barbosa et al., 2014). Increased inflammatory cytokines prior to treatment may predict non-response (Becking et al., 2013). Tumor necrosis factor-alpha is associated with both metabolic syndrome and bipolar disorder (Prossin et al., 2013) who pointed out the possible utility of TNF- α antagonists in the treatment of mood disorders. High levels of cytokines (Walker et al., 2014) not only underlie non-response but also predict the onset of manic symptoms and C-reactive protein levels are elevated in unipolar depressed men who develop manic symptoms. Activated microglia in the kynurenine pathway during drug addiction and diabetes trigger an alternate route of tryptophan metabolism that increase production of the toxic quinolinic acid and ultimately reduce overall serotonin availability (Kovacs, 2012; Watkins et al., 2014); while TNF-alpha may induce mitochondrial dysfunction (Najjar et al., 2013). AMP-activated protein kinase signalling increases neurotrophic factors, decreases inducible nitric oxide synthase and oxidative stress to protect oligodendrocytes that restore CNS functions in an experimental autoimmune encephalomyelitis model (Paintlia et al., 2013).

Cholinergic Mechanisms in Diabetes and Bipolar Disorder

There may be decreased activities of cholinesterase in the brain during diabetes with increased accumulation of acetylcholine, due to insulin and lipid peroxidation, which may lead to cholinergic-induced hyper-activity, convulsions and epilepsy (Ashokkumar et al., 2006). Hyperinsulinaemia may decrease brain acetylcholinesterase, Na⁺-K⁺-ATPase and Mg²⁺-ATPase (Chen et al., 2009). Cholinergic excess has been

implicated as a mechanism for the causation of depressive disorder (Renshaw et al., 1997) though Craft and Watson (2004) had found decreased brain acetylcholine levels in insulin resistance. Valproate treatment normalises mania-like behavioural deficits by enhancing M₁-receptor-ERK pathway signalling (Chiu et al., 2013). Administration of N-benzoyl-D-phenylalanine and metformin attenuates brain acetylcholinesterase dysfunction in neonatal streptozotocin-diabetic rats.

Recently, (Mulherin, 2011), metformin was found to increase glucagon-like peptide-I (GLP-I), which may decrease alcohol craving (Shirazi et al., 2013), by a stimulant action on the parasympathetic M₃-cholinergic receptors and on gastrin releasing peptide.

There is upregulation of hippocampal $\alpha 7$ acetylcholine receptor levels in patients with bipolar disorder but not in those with schizophrenia or major depressive disorder (Thomsen et al., 2011; Varela et al., 2013) but this could be an adaptive mechanism. Acetylcholine has been associated recently with upregulation of the nutrient sensor, AMPK, and with mammalian target of rapamycin (mTOR) inhibition. Metformin could increase acetylcholine release by AMPK activation (Dong et al., 2010), and increase also nicotinic acetylcholine receptors and GABA (A) (Zhao et al., 2013). Alpha 7 nicotinic acetylcholine receptor-selective agonists reduce weight gain and metabolic changes in mouse models of diabetes supporting the cholinergic anti-inflammatory pathway that act on $\alpha 7$ receptors expressed on macrophages and immune cells making its agonists to be helpful in diabetes mellitus. Elevated levels of butyrylcholinesterase and acetylcholinesterase may predict the development of type 2 DM and Alzheimer's disease (Rao et al., 2007).

The pathology in Alzheimer's disease is apoptosis of cholinergic neurons in basal fore-brain with decreased cholinesterase activity in other brain areas and anti-cholinesterases may be used as adjunct medication because they reduce rate of degradation of acetylcholine, have off-target effects such as increasing growth factors, for example, growth hormone and insulin-like growth factor-I. They also decrease glutamate excitotoxicity and increase phosphatidylinositol-3-kinase/protein kinase B (Akt) signalling to promote neuronal survival (de la Monte, 2012).

Noradrenergic mechanisms in insulin resistance, substance use disorder and mania

There is reduction in neuronal reuptake of noradrenaline and lower levels of monoamine oxidase A (MAO_A) in type 2 diabetes mellitus resulting in increased central sympathetic outflow (Straznicky et al., 2012) in tandem with decrease in ethanol-induced sleep in transgenic mice lacking MAO_A (Popova et al., 2000). Cerebro-spinal fluid norepinephrine metabolite (3-methoxy-4-hydroxy-phenylglycol (MHPG) is elevated in mania patients

compared to the dopamine metabolite, homovanillic acid (HVA) or the serotonin metabolite, 5-hydroxyindoleacetic acid (HIAA) implying an excessive, abnormal noradrenergic activity in mania (Swan et al., 1983). Higher urinary catecholamine concentration in adulthood predicts higher levels of drug use (Brody et al., 2014). Levels of MHPG are decreased by lithium (Ostrow et al., 1984). Normally, there is activation of the norepinephrine transporter by insulin (Apparsundaram (2001).

Dopaminergic activity in bipolar disorder, drug addiction, epilepsy and diabetes

Dysfunctional processing of reward-based feeding through the dopaminergic system is a potential contributor to the obesity epidemic and likely contributes to the co-morbidity of the metabolic syndrome and mental health diseases including drug addiction (Nousen et al., 2013; Volkow et al., 2009; Zhuang et al., 2001; Graham et al., 2013) and epilepsy (Chen, 2006). Drugs of abuse and food cause substantial modifications to the mesolimbic dopaminergic system (Baik, 2013). Dopamine D₃R through cross-talk with dopamine D₁R is involved in induction and expression of behavioural sensitization to levodopa (Sokoloff et al., 2001) and dopamine D₃R antagonists are reported to be beneficial for drug addiction (Le Fall et al., 2014). Dopaminergic (D₂R) stimulation activates glycogen synthase kinase-3 β (GSK3 β) (Beaulieu et al., 2011) while serotonergic activity contributes to the inhibitory control of GSK3 β (Beaulieu, 2012; www.pharmatutor.org). Indirect activation of the dopamine D₁ receptor by cocaine increases nitric oxide production and this contributes to its behavioural effects (Winick-Ng et al., 2012). The dopamine hypothesis of bipolar disorder implicates dopamine dysregulation syndrome and suggests increased dopaminergic drive in mania and the converse in depression. Bipolar disorder may be a cyclical process, where increased dopaminergic transmission is responsible for the manic features and receptor down-regulation may correspond to the depression phase (Berk et al., 2007). Pronounced hyperactivity, caffeine hypersensitivity and reduced sleep are typically observed in dopamine transporter (DAT) knock-out animals (Holst et al., 2014) and sleep-deprivation may induce supersensitivity of dopaminergic receptors in the rat brain (Tufik et al., 1978; Palma et al., 2009; De Laurentis et al., 2002; Troncone et al., 1998). Prostaglandin E₂ may amplify D₁ and D₂ receptor signalling (Kitaoka et al., 2007; Di Marzo and Piomelli, 1992). There is increased D₂R availability in obese subjects (Dunn et al., 2012) and insulin sensitivity is negatively associated with D₂R availability. Sustained expression of PGC-1 α in the rat nigrostriatal system selectively impairs dopaminergic function (Ciron et al., 2010) and this and PPAR α (Melis et al., 2011; 2013) may synergistically serve to antagonise the essential role

of SIRT1 (HDAC 3)-FOXO3a signalling in the nucleus accumbens in cocaine and morphine addiction (Ferguson et al., 2013; Ferguson et al., 2015). Cocaine increases expression of SIRT1 which probably increases NF-kappa β to maintain the addiction state (Russo et al., 2009) and resveratrol-induced activation of SIRT1 enhances the motivational properties of cocaine (Kenny, 2011). Chronic valproate (Ramadan et al., 2011) and metformin (Xu et al., 2014; Hristova, 2011) may block D2-like receptor-mediated brain signalling via arachidonic acid. Cannabinoid CB2 agonists modulate midbrain dopamine neuronal activity and dopamine-related behaviour in mice (Zhang et al., 2014; Oriaifo et al., 2015).

The immature dentate gyrus may be an endophenotype of bipolar disorder and epilepsy (Hagihara et al., 2013), mediated partly by hyperdopaminergic signalling which dysregulates GSK-3 signalling, and metformin may upregulate neurogenesis in the dentate gyrus after dematuration by high-fat diet (Yoo et al., 2011).

Serotonergic mechanisms in bipolar disorder and cardiometabolic risk

Drugs with agonist effect at serotonin 5-HT_{1A} receptors such as lithium and ziprasidone including cannabinoids are useful for management of bipolar disorder (Nemeroff et al., 2005; Muraki, 2001; Bambico et al., 2014; Ashton et al., 2005). The hypothesis of dysregulation of the serotonergic system in bipolar disorder is supported by the decrease in 5-HT_{1A} mRNA levels in subjects with major depressive disorder and decrease in 5-HT_{2A} mRNA in subjects with bipolar disorder (Lopez-Figueroa et al., 2004). There is also decrease in 5-HT_{2A} mRNA in the hippocampal formation in subjects with bipolar disorder plus significant reductions in major serotonin metabolite, 5-HIAA, in frontal and parietal cortex in bipolar patients. Also, mechanisms that increase the expression of BDNF may decrease the serotonin transporter (SERT) and increase serotonergic signalling (Deltheil et al., 2008). This may be a mechanism to explain the effects of the BDNF-mimetic agents such as lithium, valproate, metformin and calorie-restriction (Araya et al., 2008) in upregulation of serotonergic signalling.

Modulation of the serotonergic system might be implied in epileptogenesis in temporal lobe epilepsy (Schenkel et al., 2011). Metformin may increase serotonergic neurotransmission by its inhibition of the serotonin transporter, SERT, (Han et al., 2013) and activation of BDNF release (Yanev et al., 2013; Yoo et al., 2011; Hristova, 2011) which in turn inhibits SERT (Deltheil et al., 2008). Metformin may antagonise TNF-alpha upregulation of SERT (Nichols, 2009). It has been reported that metformin elevates the activity of tyrosine kinase receptors and may amplify BDNF

signalling (Hong et al., 2009), the cortical levels of which are low in epilepsy (Chaldakov et al., 2014) and drug addiction (Whitfield et al., 2011). Metformin's activation of insulin release (Gunton et al., 2003; Holland et al., 2004) enhances central serotonergic neurotransmission (Horacek et al., 1999), partly, due to the observation that insulin increases the movement of tryptophan through the blood-brain-barrier. Conversely, stimulation of 5-HT neurotransmission by metformin and cannabinoid CB2 agonists enhance the release of and sensitivity to insulin (Paulmann et al., 2009; Pazos et al., 2013; Goodnick et al., 1995) and mitochondrial biogenesis (Rasbach et al., 2010). Serotonergic agonists attenuate the actions of GSK-3 beta and enhance Akt opposite to drugs such as amphetamine and levodopa which activate GSK-3 beta and inhibit Akt (Beaulieu, 2012).

The calorie restriction-mimetics, metformin (Onken and Driscoll, 2010) and cannabinoids (Oriaifo et al., 2015), may increase serotonin turn-over in the brain (Bambico et al., 2014; Schweiger et al., 1989). This enhances neural plasticity by effects on the serotonin transporter in a manner similar to the serotonin agonists, the selective serotonin reuptake inhibitors (Riddle et al., 2013)

Metformin also prevents decreases in synaptophysin levels (Li et al., 2012). GSK-3 inhibitors (Horike et al., 2008), such as metformin and valproate, result in accumulation of synapsin- I which is a protein involved in synaptic vesicle docking at growth cone-like areas (Manji et al., 2003). The calorie-mimetic, metformin, (Martin-Montalvo et al., 2013) may shift expression patterns of mice towards those on calorie restriction and increase BDNF levels (Araya et al., 2008) necessary for prevention of pancreatic exhaustion (Yamanaka et al., 2008) and upregulation of synaptogenesis (El-Sayed et al., 2014).

Inositol and neuropsychiatric illnesses

Inositol has been shown to have antidepressant properties (Einat et al., 2001) and myo-inositol treatment prevents GABA_A receptor subunit alpha-4 and alpha-2 degradation (Solomon et al., 2013) and halts reduction of calcium-dependent calmodulin protein kinase II (CaMKII) (Solomon et al., 2010). Inositol lipid signalling is important in synaptic activity, neuronal plasticity and anti-epileptogenesis (Bazan and Musto, 2009). The coupling between insulin action and the release of D-chiro-inositol-containing inositolphosphoglycan (DCI-IPG) mediator is selectively impaired in obese women with polycystic ovary syndrome (PCOS) which may contribute to the insulin resistance and symptoms of bipolar disorder in these women (Agarwal et al., 2011; McIntyre et al., 2003; Baillargeon et al., 2010) that may be responsive to valproate and metformin. Metformin therapy increases insulin-stimulated release of D-chiro-inositol-containing inositol phosphoglycan mediators in women with

polycystic ovary syndrome (Baillargeon et al., 2004) which may have genetic overlap with bipolar disorder and corrects the D-chiro-inositol/myo-inositol imbalance.

Role guanine nucleotide (GTP)-binding proteins (G-Proteins) in bipolar disorder and metabolic syndrome

New evidence suggests abnormalities in the interaction between the neurotransmitter systems and G-proteins in bipolar disorder and diabetes. Considerable evidence exists demonstrating a link between inhibitory guanine nucleotide binding-proteins (G-proteins) and G-protein-coupled receptor (GPCR) signalling in insulin-responsive tissues and the pathogenesis of obesity, type 2 diabetes mellitus and beta-cell dysfunction (Kimple et al., 2014). The insulin sensitizer, metformin, is able to disrupt crosstalk between G-protein coupled receptors and insulin receptor signalling systems (Kisfalvi et al., 2009). Also, enhanced receptor to G-protein coupling leads to an increase in the active state of the G-proteins with attendant exaggerated trans-membrane signalling (Friedman et al., 2002), an effect which is abrogated by lithium (Avisar and Schreiber, 1989; Risby et al., 1991) and this may explain the antimanic and antidepressant effects of lithium. For example, α_{2A} -adrenoceptor (which binds to inhibitory G-proteins) sensitivity is increased in the frontal cortex of suicide victims with mood disorders (Gonzalez-Maeso et al., 2002).

GABAergic mechanisms in bipolar disorder and Alzheimer's disease

There is reduced number of somatostatin- and parvalbumin- positive cells (a marker of mature fast-spiking interneurons), GABAergic gene expression, NPY mRNAs in regions that participate in mood regulation, namely the anterior cingulate cortex, hippocampus, entorhinal and dorsolateral prefrontal cortex, all suggesting that bipolar disorder and schizophrenia might be associated with decreased levels of gamma-aminobutyric acid (GABA) neurotransmission (Kuromitsu et al., 2001; Mellios et al., 2009; Wang et al., 2011; Gandal et al., 2012), though epigenetic mechanisms expressed in basal ganglia GABAergic neurons differentiate schizophrenia from bipolar disorder (Veldic et al., 2007). This may be the cause of the disrupted synchronisation and integration of cortico-hippocampal circuits. GABAergic dysfunction may be attenuated by the master regulator of mitochondrial biogenesis, PGC-1 alpha (Lucas et al., 2010) which rescues paralbumin deficiency. Additionally, the epileptogenic focus has been demonstrated to have biochemical defects in metabolism of acetylcholine, glutamic acid, GABA and potassium. There may also be enhanced NMDA conductance (Bazan et al., 2002). The onset of ictus is heralded by

exhaustion of pre-synaptic release of GABA and unopposed increased glutamatergic responses (Zhang et al., 2012). The enhancement of GABAergic neuron numbers, neurite outgrowth and phenotypic expression via increases in the neuronal differentiation of neural stem cell may contribute to the therapeutic effects of valproate in the treatment of bipolar disorder (Laeng et al., 2004). Cannabinoids may regulate GABAergic signalling in a CBI R-independent manner (Golovko et al., 2015) while metformin may enhance GABA-B receptor activation of inwardly-rectifying potassium channels and inhibit calcium channels to attenuate seizures (Kuramoto et al., 2007).

There is also reduction in neuronal calbindin immunoreactivity in diabetes (Yi, 2013) and Alzheimer's disease (Kook et al., 2014). Calbindin buffers free calcium (Ca^{2+}) and prevents neuronal apoptosis. Removal of calbindin from amyloid precursor protein/presenilin in transgenic mice aggravates Alzheimer's disease (AD) pathogenesis, suggesting that calbindin has a critical role in AD pathogenesis.

Glycogen Synthase Kinase-3 beta: role in insulin resistance, Seizure Activity, drug addiction and bipolar disorder

Metformin is a glucagon-like peptide-1 (GLP-1) enhancer and sensitizer (Kim et al., 2014; Mulherin, 2011; Cho and Kieffer, 2011) acting via cholinergic M_3 receptors and PPAR- α . GLP-1 which activates eNOS (Ding and Zhang, 2012) is neuroprotective (Darsalia et al., 2012; Shirazi et al., 2013), shows promise for treatment of bipolar disorder and Alzheimer's disease (McIntyre et al., 2013; Holscher, 2010), psychosis (Dixit et al., 2013) and addiction disorders (Shirazi et al., 2013; Engel and Jerlhag, 2014; Skibicka, 2013). It has been linked to modification of glycogen synthase kinase-3 (GSK-3) (Gao et al., 2011) whose overexpression or overactivation induces a series of changes which are hallmarks of Alzheimer's disease, bipolar disorder, epileptogenesis, type 2 diabetes mellitus (Sutherland, 2011; Li et al., 2002; Lee et al., 2012; Nikoulina et al., 2000) and substance addiction (Xu et al., 2011; Parkitna et al., 2006; Li et al., 2013).

Metformin upregulates adenosine triphosphate

Adenosine triphosphate (ATP) may be required for inactivation of GSK-3 beta by phosphorylation (Sutherland et al., 1993) and metformin upregulates ATP levels by switching on ATP-producing catabolic pathways (Zhang et al., 2006). Metformin, via AMPK activation of protein kinase B (Akt), also inactivates GSK-3 beta (Horike et al., 2008) and activates cyclic adenosine monophosphate response element binding protein

(CREB) (Sag et al., 2008). Adenosine monophosphate-activated protein kinase (AMPK) activators, such as metformin, activate Akt which is accompanied by increased inhibitory phosphorylation of GSK-3 beta and activation of CREB (Sag et al., 2008). Another way by which metformin, which increases extracellular ATP concentration (Piwkowska et al., 2013), could also indirectly inhibit GSK-3 beta is through upregulation of the G-protein coupled purinergic (ATP) P2 receptor (Neary and Kang, 2006) and P2X7 receptor (Ortega et al., 2010).

Brain-derived neurotrophic factor, which is upregulated by metformin, also inhibits GSK-3 beta by inhibitory phosphorylation (Mai et al., 2002).

The activities of TLRs are regulated by glycogen synthase kinase-3 (GSK3) (Martin et al., 2005; Wang et al., 2011) and GSK-3 beta expression is increased in type 2 diabetes mellitus (Nikoulina et al., 2000). It may be crucial for epileptogenesis (Lee et al., 2012). In hyperinsulinaemia, oxidative stress, high glucose and GSK-3 beta may activate nuclear factor-kappa β to induce matrix metalloproteinase-9 (Zhong and Kowluru, 2013; Zhong et al., 2014) which increases excitability to leptazol-induced seizures (Wilczynski et al., 2008). Non-specific inhibitors of glycogen synthase kinase such as metformin and cannabinoids may suppress the production of interleukin-1 beta, interleukin-6, interleukin-12 and tumor necrosis factor whilst enhancing production of interleukin-10. Epilepsy-related lafora disease is caused by defective mutation in laforin which inactivates GSK3 at Ser9 from the N-terminus (Cho, 2011).

There is also evidence for antimanic efficacy of glycogen synthase kinase-3 beta (GSK-3 beta) inhibitors in animal models of mania (Kalinicher and Dawson, 2011). Valproate, carbamazepine and ziprasidone produce selective inhibition of rearing hyperactivity in mice. Valproate and lithium inhibit GSK-3 beta directly or indirectly (Kim et al., 2005; Huang et al., 2014; Prickarets et al., 2006) via stimulation of protein kinase B (Akt-I). Glycogen synthase kinase-3 beta regulates endoplasmic reticulum (ER) stress-induced expression of the apoptotic protein, CHOP, in neuronal cells and its inhibitors reduce the expression of CHOP (Meares et al., 2012).

Valproate, by inhibiting GSK-3 beta, increases the expression of chaperones that assist in the folding of proteins including glucose regulated protein 78 or binding immunoglobulin protein (GRP 78/BiP), GRP 94, protein disulphide isomerase (PDI) and calreticulin as well as the cytosolic chaperone heat shock protein 70 (HSP70) (Kim et al., 2005; Huang et al., 2014), thereby protecting cells from ER stress-induced lipid accumulation and lethal damage induced by unfolded/misfolded proteins.

Hyperglutamatergic excitotoxicity in bipolar disorder, substance addiction, epilepsy and diabetes mellitus

Hyperglutamatergic excitotoxic-mediated increases in intracellular calcium and lipid messengers such as arachidonic acid (AA) and platelet-activating factor may lead to neuronal death and reactive gliosis, resulting in the formation of a glial scar which becomes the epicentre of an epileptogenic hyperexcitable focus (Bazan et al., 2002). Dysregulation of NMDA and CREB signalling is also important in drug addiction (Li et al., 2013; Pandey et al., 2004), bipolar disorder (Chen et al., 2014) and epilepsy where seizures induce increases in intracellular calcium (Raza et al., 2001). BDNF suppressed cocaine prime-induced increase in extracellular glutamate levels in the nucleus accumbens (McGinty et al., 2010). The specificity protein transcription factor (SP₄), which regulates mitochondrial key glutamatergic receptor subunit genes (Johar et al., 2013), is reduced by NMDA receptor signalling (Saia et al., 2014; Pinacho et al., 2011) and may be normalised by lithium and valproate (Arinze et al., 2013), while its degradation is promoted by store-operated calcium entry which could be a consequence of mitochondrial dysfunction (Lalonde et al., 2014; Kato, 2008). SP₁ modulates the expression of metformin transporters, such as the organic cationic transporters, and genetic variants in this specificity protein I have been found associated with metformin response (treatment HbA1c), with homozygous carriers having 24% reduction in apparent clearance (Goswami et al., 2014). Also, the endoplasmic reticulum (ER) stress response protein, X-box binding protein I (XBPI), which is neuroprotective, prevents the accumulation of free calcium (Ca²⁺) in the cytosol (Casas-Tinto et al., 2011).

Tumor necrosis factor-alpha, interleukin-1 β and interleukin-6 mechanisms increase glutamate release (Weaver-Mikaere et al., 2013; Viviani et al., 2003; Orellana et al., 2005). Metformin prevents mitochondrial permeability transition induced by calcium (Guigas et al., 2004) and antagonises PKC- and calcium-induced detrusor overactivity in a model of obesity-associated with insulin resistance in mice (Leina et al., 2012). AMPK activation by metformin and valproate also protects against glutamate-induced cell death (Kim et al., 2013; Culmsec et al., 2001; Hashimoto et al., 2002). AMPK activation dampens the excitatory effect of NMDA via potentiation of potassium-ATP (K-ATP) current (Shen et al., 2014; Kirpichnikov et al., 2002) and opposes the inhibitory effect on K⁺ (Kv) channels by GSK-dependent phosphorylation (Wildburger and Laezza, 2012). Mild mitochondrial uncoupling induced-protection against neuronal excitotoxicity requires AMPK activity (Weisova et al., 2014) which decreases with aging, contributing to mitochondrial dysfunction (Khatri et al., 2013). CREB which regulates GLUT3 is reduced in AD because

overactivation of calpain in neuropsychiatric diseases/ cardiometabolic diseases by calcium proteolyses CREB (Khatri et al., 2013). High –fat diets induce changes in hippocampal glutamate metabolism and neurotransmission (Valladolid-Acebes et al., 2012) who showed that glial glutamate carriers were upregulated while glutamate-degrading enzymes, glutamine synthase and GABA-decarboxylase, were downregulated. Glutamatergic pre-ictal discharges are at the transition to seizure in human epilepsy (Huberfeld et al., 2011).

Role of oxidants in drug addiction and neural dysfunction

Mitochondrial calcium is modulated by reactive oxygen and nitrogen species and sustained Ca^{2+} increase generates reactive oxygen species (ROS) and cell death (Manzl, 1992). Additionally, a hyperactive mammalian target of rapamycin (mTOR) signalling and drugs of abuse increase generation of ROS (Potter et al., 2010; Dietrich et al., 2005) and mTOR inhibitors block cocaine-induced locomotion sensitization (Wu et al., 2011; Dayas et al., 2012). AMPK activation suppresses ER stress by inhibiting NAD(P)H oxidase-derived ROS, a well-known stress initiator (Dong et al., 2010). Cannabidiol may target mitochondria to regulate intracellular Ca^{2+} levels (Ryan et al., 2009) and suppress epileptogenesis in a cannabinoid CB_1 -receptor independent manner (Jones et al., 2010). Oxidants such as superoxide, hydroxyl radicals and lipid hydroperoxides (ROS) are now to stimulate signal transduction such as Ca^{2+} signalling and phosphorylate kinases such as the oxidative stress response kinase (Geng et al., 2009). The O subclass of the forkhead family of transcription factors, particularly FOXO 3a, protects from oxidative stress by upregulating antioxidants such as catalase and manganese superoxide dismutase (MnSOD) (Nicolli and Partridge, 2012). MnSOD is important in maintaining intracellular ROS and redox balance and modulates the activation of several redox-sensitive transcriptional factors such as NF-kappa β (Zhang, H (Sfrbm.org)). ROS production by mitochondria leads to further DNA damage and decrease in mitochondrial function, impairing mitochondrial function in AD, for example. There is a link between ROS-induced DNA damage and neurodegeneration (Kamatet al., 2013).

Sterol Regulatory Element Binding Protein- I c in Mania, Seizures and Diabetes Mellitus

All antidepressants activate sterol regulatory element binding protein- I c (SREBP-Ic), which induce lipogenic genes, to different extents. Especially antidepressants such as imipramine and fluoxetine, which induce manic switch responsible for bipolar disorder IV, activate SREBP-I c. In this regard, there is functional similarity

between antipsychotics and antidepressants (Raeder et al., 2006). Mood stabilisers such as lithium and valproate are known to downregulate SREBP-I c (Raeder et al., 2006). Polymorphisms in SREBP1 and SREBP2, two antipsychotic activated transcription factors controlling cellular lipogenesis, are associated with schizophrenia (Le Hellard et al., 2008) and with type 2 diabetes mellitus (Liu et al., 2008). SREBP activation is an essential step in NMDAR-mediated excitotoxic neuronal death (Taghibiglou et al., 2009) and DNA microarray data show that stearoyl-CoA desaturase-I, a SREBP1a target gene, is upregulated in human temporal lobe epilepsy (Arion et al., 2006). Also, uric acid promotes lipogenesis through overexpression of acetyl-CoA carboxylase-I and fatty acid synthase via activation of SREBP-I c and this is antagonised by metformin (a known blocker of SREBP-I c) (Choi et al., 2014). AMPK-activated protein kinase is required for metformin inhibition of SREBP-I c mRNA and nuclear SREBP-I c protein (Yang et al., 2009). The hepatic expression of SREBP-I c is activated by insulin (Foretz et al., 1999) and this may contribute to insulin-associated weight gain.

The Na, K-ATPase hypothesis for bipolar disorder, epilepsy and alcohol abuse: hyperglycaemia-induced activation of the endogenous digitalis system

The decline in Na, K-ATPase pump activity with age is paralleled by age-related increase in intracellular sodium with concomitant increase in neuronal excitability. Epilepsy and manic symptoms are related to decrease in Na, K-ATPase pump activity (Martinc et al., 2012; Parisi et al., 2008; El-Mallakh et al., 1993) which might decrease GABA activity. Reinforcing effects of ethanol as well as its voluntary consumption may be affected by the digitalis system (Bagrov et al., 2002). Insulin deficiency leads to hyperglycaemia, oxidative stress and the pathological activation of the endogenous digitalis system and renin-angiotensin system (Rosta Klara, 2009). Diabetes is accompanied by Na, K-ATPase (NKA) dysfunction. Activity of NKA is lower in diabetic animals (44% lower), while metformin increases the amount of NKA isoform in the plasma membrane fraction (Rosta Klara, 2009). Activation of AMP-activated protein kinase stimulates Na, K-ATPase activity in skeletal muscle cells (Benziane et al., 2012) and this may be beneficial in epileptogenesis prevention.

Autophagy enhancers may be protective in bipolar disorder, epilepsy and type 2 diabetes mellitus

Insulin resistance, which increases the insulin-like growth factor (IGF) - insulin receptor (IR) crosstalk, impairs memory and is a risk factor for the deposition of A β proteins implicated in Alzheimer's disease (AD). Reduced insulin signalling is a hall-mark of AD (Nicolli and Partridge, 2012). Inhibition of the mammalian target of

rapamycin (mTOR) signalling and its downstream target, S6KI coupled with suppression of the IGF – IR signalling (Sarfstein et al., 2013), by metformin increases insulin sensitivity, induces autophagy (Perez-Revuelta et al., 2014; Renna et al., 2010) and may be anti-epileptogenic (Loscher et al., 2010).

Induction of autophagy helps neurons clear abnormal protein aggregates, enhances cellular tolerance to various stresses and enhances survival. Autophagy is a cellular catabolic pathway by which long-lived proteins and damaged organelles are targeted for degradation by autophagosomes (Gammoh et al., 2012; Heras-Sandovul et al., 2014). Metformin activation of the survival PI3K/Akt pathway inhibits mTOR activity, thereby inducing autophagy. Valproic acid also inhibits mTOR signalling and induces autophagy (Renna et al., 2010). (Also, metformin activation of AMPK or liver kinase B results in mTOR signalling inhibition (Perez-Revuelta et al., 2014). Activation of protein phosphatase 2A activity lowers tau phosphorylation both in vitro and in vivo and leads to increased dephosphorylation of protein phosphatase 2A-dependent tau epitopes. This mechanism also decreases the ratio of phosphor-Ser 129 alpha-synuclein to total alpha-synuclein in the brain of mice, processes beneficial in AD and Parkinson's disease (Perez-Revuelta et al., 2014; Kickstein et al., 2010); and also in diabetes which may reflect an early stage of amyloid pathology (Alexander et al., 2011).

Furthermore, glucagon induces Class II histone deacetylase which activates FOXO deacetylation and nuclear translocation. Inhibition of class II histone deacetylase by metformin-dependent activation of AMPK results in inhibition of FOXO target genes and lowering of blood glucose (Mihaylova et al., 2011). Valproic acid also inhibits histone deacetylase (Phiel et al., 2001). Histone deacetylase inhibition potentiates the ability of mTOR inhibitors to induce autophagy (Dong et al., 2013), for example, pointing to a possible metformin + valproate synergism.

Role for adenosine, adenine nucleotides in epilepsy, bipolar disorder, diabetes mellitus and alcohol addiction

Drugs that upregulate adenosine and adenosine kinase inhibitors are important for anti-epileptogenesis (Boison, 2008) with the caveat that adenosine may contribute to alcohol-induced ataxia. Adenosine, which is important for the efficacy of the ketogenic diet, is upregulated by metformin (Paiva et al., 2009; Vignozzi et al., 2014; Masino et al., 2009) which increases the levels of adenosine monophosphate (AMP) that can be converted to adenosine, and also inhibits adenosine monophosphate deaminase (AMPD) for its inhibition of glucose transport and blood glucose lowering effect (Ouyang et al., 2011). There is raised serum adenosine

deaminase level in non-obese type 2 diabetes mellitus (Khemka et al., 2013) who pointed out that interaction between adenosine deaminase and dipeptidyl peptidase-4 (DPP-4) can lead to T-cell proliferation and increased cytokine release. This seems to be holding fort compared to other proposals for the glucose-lowering effect of metformin.

There is upregulation A2A adenosine receptors in platelets from bipolar disorder patients under treatment with typical antipsychotics which are most commonly used for bipolar disorders (Trincavelli et al., 2012), and here, there is antagonistic interactions between adenosine A2A receptors and dopamine D2 receptors (Martini et al., 2008; Masino et al., 2009). Pre-synaptic activity-dependent release of adenosine, through activation of adenosine A2A receptors, facilitates BDNF model of synaptic transmission in hippocampal slices (Diogenes et al., 2004). There is also antagonistic interactions between adenosine A1 receptors and dopamine D1 receptors (Popoli et al., 1996). Adenosine is known to tonically inhibit neuronal excitability (Masino et al., 2009), attenuate hyperdopaminergic signalling (Shen et al., 2014; Movsessian, 2005) and promote sleep by increasing slow-wave sleep and increasing latency to enter paradoxical or rapid-eye-movement (REM) sleep (Masino and Geiger, 2009; Kotagal and Yardi, 2008; Diaz-Negrillo, 2013). Adenosine augmentation ameliorates psychotic and cognitive endophenotypes of schizophrenia (Shen et al., 2014); and adjuvant purinergic modulators have been found helpful in bipolar disorder (Hirota and Kishi, 2013) where reduced adenosinergic activity may be related to initiation of manic behaviour (Machado-Vieira et al., 2002).

At low concentrations of NMDA, ATP P2X7 receptor agonists such as BzATP, exhibit additive effects with both NMDA and BDNF to prevent cell-death in cerebellar granule cells induced by PI3K inhibitors (Ortega et al., 2010; Bhave et al., 1999). Extracellular adenosine through conversion to adenosine monophosphate (AMP) (Ouyang et al., 2011) activates AMPK, a process linked to LKBI, and mediated by nucleoside transporters (Goncalves et al., 2010). Calcium-calmodulin dependent protein kinase II (CaMKK II) is the kinase involved in ATP (nucleotide)-mediated AMPK activation (Goncalves et al., 2010) who noted that metformin may induce AMPK activation not dependent on AMP/ATP ratio. ATP P2X7 receptor, inhibited by alcohol (Xiong et al., 2005) but rescued by ivermectin (Norenberg et al., 2012), activates AMPK to inhibit mTOR (Bian et al., 2013) important for autophagy induction and it may also be coupled to GSK-3 inhibition and neuroprotection in cerebellar granule cells (Leonet et al., 2006; Ortega et al., 2009). P2XRs and serotonergic signaling have important roles in modulating the activity of dopaminergic neurons important for controlling ethanol intake (Abbracchio et al., 2009).

In the synaptic P2X7 receptor regenerative loop hypothesis for depression and bipolar disorder (Bennet, 2007), ATP/P2X7 pathway triggers the T-cell attack on the pancreas and may also lead to bipolar disorder, when, instead of ATP/glutamate synergising with TNF-alpha to post-synaptically increase alpha-amino 3-hydroxy-5-methyl-4-propionic acid (AMPA) receptors, Toll-like receptors (TLR) activated by infections release interleukin-1 beta which decrease alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, thereby, decreasing synaptic efficacy. This may be due to the observation that ATP acts as a competitive antagonist of NMDA receptors at low glutamate concentrations and a positive allosteric modulator at high glutamate concentrations engendered by infections (Ortinau et al., 2003; Kloda et al., 2004).

The P2X7 receptor is graduating to be seen as a key point of communication between the nervous, immune and cardiovascular diseases (Skaper et al., 2009) whilst the P2Y1 receptor may be central in autocrine stimulation of human beta cells (Tengholm, 2014). Overactivation or overexpression of P2X7 receptors, however, (Skaper and Giusti, 2009) may promote TNF-alpha-induced apoptosis via activation of caspase-3 and interleukin-1 beta release. Interleukin-1 beta is a key mediator of neurodegeneration and type 2 diabetes mellitus and P2X7 receptor knock-out mice have antidepressant phenotype (Tran et al., 1999; Skaper et al., 2009).

Vasopressin V1 (b) contributes to epilepsy, mood disorders and cardiometabolic disease: the role of AMPK

BDNF (Choe et al., 2014); metformin (Bhalla et al., 1996) and valproate (Coiro and Chiodera, 1989) antagonise arginine vasopressin-induced responses in contributing to both mood disorders (Dempster et al., 2007) and seizures (Gulec and Novan, 2002) as well as to drug addiction (Zhou et al., 2012; Zhou et al., 2008); and the transition from compensated left ventricular hypertrophy to the decompensated heart (cardiac hypertrophy) (Beauloye et al., 2011; Chaltherie, 2005). These reports show arginine vasopressin to be one of the factors linking cardiometabolic and neuropsychiatric disorders.

Neurotrophins, cellular plasticity and resilience

The family of receptors known as tyrosine kinase receptors (Trks) mediate neurotrophic factor signalling. Nerve growth factor (NGF) binds to TrkA and brain-derived neurotrophic factor (BDNF) binds to TrkB (Saarelainen et al., 2003). Phosphatidylinositol-3kinase (PI-3K) is then activated; also, there is activation of mitogen-activated protein (MAP) kinase. MAP kinase cascade activation can inhibit apoptosis by inducing the

phosphorylation of Bcl-2 associated agonist of cell death (Bad) (a major pro-apoptotic protein) and increasing the expression of Bcl-2 (a major antiapoptotic protein) (Manji et al., 2003). The increased Bcl-2 expression involves cyclic adenosine monophosphate response element binding protein (CREB). Bcl-2 is neuroprotective and exerts neurotrophic effects (Manji et al., 2003). The presence of TrkB, the high-affinity receptor for BDNF, in hippocampal neural progenitor cells is required for the neurogenic and behavioural actions of antidepressant treatments (Banasr and Duman, 2009). BDNF controls dopamine D₃R expression (Guillin et al., 2001). It normalises cocaine-induced disruption of glutamatergic transmission in the nucleus accumbens and the suppressive effect of BDNF in the prefrontal cortex on cocaine-seeking is Trk receptor dependent (Whitfield et al., 2011).

Recently, studies in adipobiology (Chaldakov et al., 2010) and neuroendocrinology (Chaldakov et al., 2014) has revealed that the neurotrophic factors NGF and BDNF (important for the process of activity-dependent synaptic plasticity, dendritic spine density and cytoskeletal dynamics), are also produced by adipose tissue (Yanev et al., 2013) and that NGF-BDNF/TrkA, B dysfunction may synergistically lead to cardiometabolic and neuropsychiatric diseases. NGF is related to an enhanced upregulation of the purinergic P2X3 receptor (Liu et al., 2011) and NMDA antagonists such as ketamine and AMPA agonists increase synthesis of BDNF.

BDNF-producing haematopoietic cells, which can control appetite and energy homeostasis by migrating to the brain (Urabe et al., 2013) may represent useful tools to treat neuropsychiatric and cardiometabolic disorders such as obesity and the metabolic syndrome (Azoulay et al., 2008).

Calorie restriction potentiates the effect of metformin, cannabinoids and valproate and inhibits drug relapse behaviour.

Calorie restriction increases seizure threshold (Greene et al., 2001). The calorie-mimetics, metformin, cannabinoids and artesunate, stand to potentiate the effect of calorie-restriction (CR) in the management of epilepsy and AD where the activity of FOXO3a is reduced (Wang et al., 2015; Oriafio, 2001; Penner et al., 2012; Kim et al., 2014; Qin et al., 2008). Calorie-restriction with weight loss inhibits drug relapse behaviour (Guccione et al., 2013). It also increases insulin sensitivity by activating FOXO3a, a key regulator of insulin and IGF-I signalling. Independently, CR prevents amyloid-beta (Abeta) neuropathology in mouse models of Alzheimer's disease, results in elevation of alpha-secretase activity and induces sirtuin 1 (SIRT 1) activation (Qin et al., 2006a, 2006b).

Homocysteine is implicated in the mechanisms of cardiometabolic and neuropsychiatric illnesses

Calorie restriction attenuates the adverse CNS changes due to homocysteine (Willette et al., 2012). Homocysteine upregulates NF-kappa B signalling (Au-Yeung et al., 2006) important in drug relapse and for the rewarding effects of cocaine. It is also important in the mechanisms of type 2 diabetes mellitus (Ebesunun and Obajobi, 2010), epilepsy (Eldeen et al., 2012), bipolar disorder (Osher et al., 2004), stroke (Ma et al., 2015) and Alzheimer's disease (Morris, 2003).

CONCLUSION

Evidence reviewed substantiate that there is considerable overlap in the aetiopathogenic mechanisms of the metabolic syndrome, bipolar disorder, substance use disorder and epilepsy. This consideration may signal a common front, such as using the NF-kappa B and interleukin-1 beta antagonists, in tackling these disorders.

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