



Review

Metformin, cannabinoids and artesunate: Convergent mechanisms in cardiometabolic and neuropsychiatric disorders

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Abstract

Emerging evidence shows that there is a convergence of mechanisms amongst the calorie-restriction-mimetic drugs metformin, artesunate and the cannabinoid CB2 receptor activators such as cannabidiol in reducing the burden of cardiometabolic diseases, such as type 2 diabetes mellitus, and neuropsychiatric diseases, such as epilepsy. Mechanistically, their pharmacological actions appear to converge on endothelial nitric oxide signalling through peroxisome proliferator-activated receptor gamma coactivator-1 alpha to peroxisome proliferator-activated receptor alpha which upregulates mitochondrial biogenesis and has neuroprotective effects. Down-regulation of mitochondrial function which is a feature of type 2 diabetes mellitus may be crucial in pathogenesis of cardiometabolic and neuropsychiatric disorders. Evidence shows that chronic metformin, artesunate and cannabis administrations have overlapping or similar effects in preventing and attenuating some parameters of the metabolic or insulin resistance syndrome in a Nigerian population and in inhibiting development and progression of seizures. They thus deserve further attention as agents which may help shed more light on the links between cardiometabolic and neuropsychiatric illnesses.

Key-words: Metformin, artesunate, cannabinoid CB2 agonists, cardiometabolic, neuropsychiatric, mechanisms

INTRODUCTION

The low-grade inflammatory state constituted by obesity (Hedstrom et al., 2014) and the upregulation of pro-inflammatory cytokines in diabetes mellitus (Jia et al., 2014) impacts on development of other age-related and immune-based illnesses.

Evidence suggests that molecular defects associated with the development of diabetes also contribute to an increased risk of neuropsychiatric diseases (Cole et al., 2007). And recent epidemiological studies point to new,

unsuspected association of cardiovascular disorders with bipolar mood disorders and epilepsy, neuropsychiatric diseases with overlapping aetiopathogenetic mechanisms (Manev, 2009_A, 2009_B; Kanner et al., 2014). The possible mediators of this association, such as polymorphism in the matrix metalloproteinase-9 (MMP9) gene (Rybakowski, 2009) and microRNA-regulated (such as microRNA-132) pathways (Hebert, 2009), are being unravelled. Immune/inflammatory and cardiometabolic

Figure I: The electron transport chain for conversion of electrochemical potential energy to chemical energy in the form of ATP in the mitochondrial inner membrane

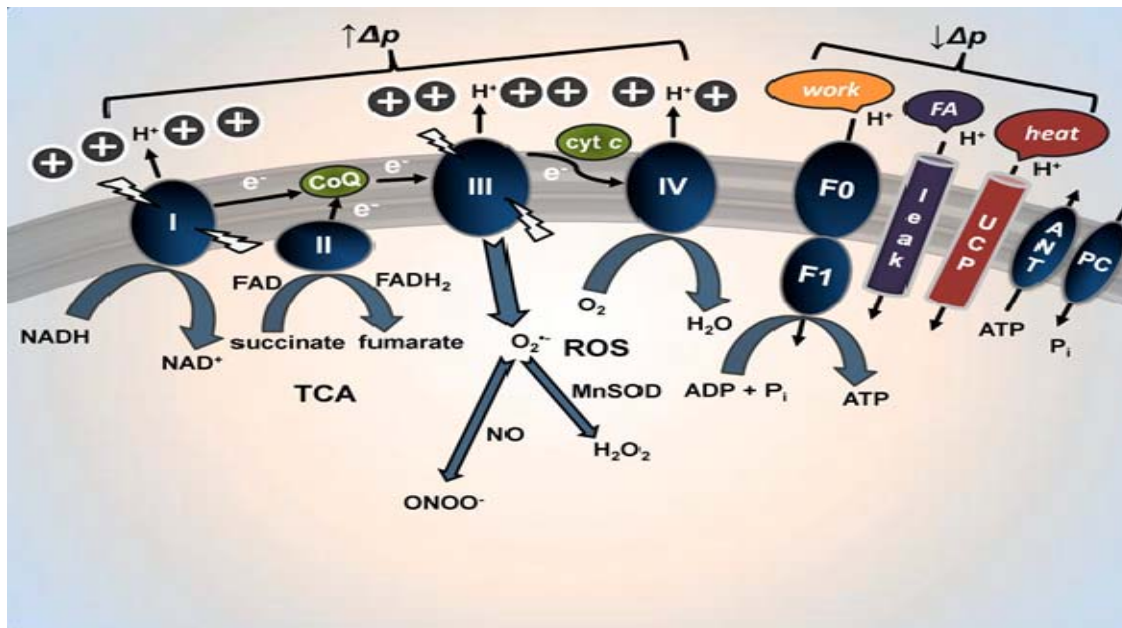


Figure I. Representation of the electron shuttle in the inner mitochondrial membrane: In the mitochondria, acetyl-CoA generated from pyruvate, β -oxidation of fatty acids and amino acids had entered the citric acid cycle (Krebs cycle) to finally generate reducing equivalents. Reducing equivalents (especially NADH) from citric acid cycle enter the electron transport chain (ETC) in the inner mitochondrial membrane to undergo oxidative phosphorylation (OXYPHOS) which eventually converts electrochemical potential energy to chemical energy in the form of ATP. OXYPHOS in the mitochondrial inner membrane generates 17 times more ATP than glycolysis in the cytosol. ETC consists of I - V complexes that transfer electrons, pump protons outwardly, and create proton motive force (Δp). **Complex I:** catalyses oxidation of nicotinamide adenine dinucleotide (NADH), **complex II:** oxidizes succinate to fumarate. Ubiquinone (CoQ) as a cofactor accepts electrons from complexes I and II, and carries them to complex III; **Complex III:** hydrogen peroxide and peroxynitrite are formed. The second mobile carrier cytochrome C (cyt c) move electrons from complex III to complex IV. **Complex IV:** O_2 is finally reduced to water. **Complex V:** The proton gradient is primarily consumed by F₀F₁ ATP synthase for ATP synthesis from ADP and inorganic phosphate Pi. Secondary consumers causing decreased Δp are uncoupling proteins (UCPs), UCP1 is present in brown adipose tissue where it maintains adaptive non-shivering thermogenesis; UCP2 (widely distributed) and UCP3 (present in skeletal muscle) regulate ROS levels, fatty acid metabolism and insulin secretion (Samec et al., 1999). Proton leak is mediated e.g. by FAs. Transport of ADP and ATP across the membrane is enabled by adenine nucleotide translocator (ANT); mitochondrial phosphate carrier protein (PC) catalyses movement of Pi into the mitochondrial matrix. Simultaneously, electron transport is accompanied by generation of reactive oxygen species (ROS), **the highest amount of superoxide ($O_2^{\bullet-}$) is formed by complexes I and III.** $O_2^{\bullet-}$ can be further transformed by manganese superoxide dismutase (MnSOD) to H_2O_2 , or can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$). $O_2^{\bullet-}$ production leads to increased mitochondrial conductance through UCPs. (Adapted from Hroudova et al., 2013, INTECH open science)

risk factors may be common endophenotypes of both physical and psychiatric illnesses (Krishnadaset al., 2014).

Metformin, cannabinoids and artesunate attenuate factors of the metabolic syndrome

Previous prospective report by author (Oriaifo, 2001) spelt out that heavy cannabis use was important in the link between cardiometabolic functions and neuropsychiatric

functions for it upregulated lipid oxidation, lowered blood cholesterol and showed significant effect in glucose regulation and anti-fatigue (anti-depressant) mechanisms. This report on the effect of cannabis use on cholesterol homeostasis and type 2 diabetes mellitus has been corroborated (Rajavashisthet al., 2012; Penneret al., 2013) who found in retrospective studies that cannabis use was associated with lower levels of glucose, fasting insulin and smaller waist circumference. Priestley et al. (2015) observed that cannabis acted via the PPAR alpha receptors like the cholesterol-lowering

Figure II: Metformin, artesunate and cannabinoid CB2 receptor agonists upregulate Akt-eNO signalling to PPAR alpha to enhance mitochondrial biogenesis and lipid oxidation

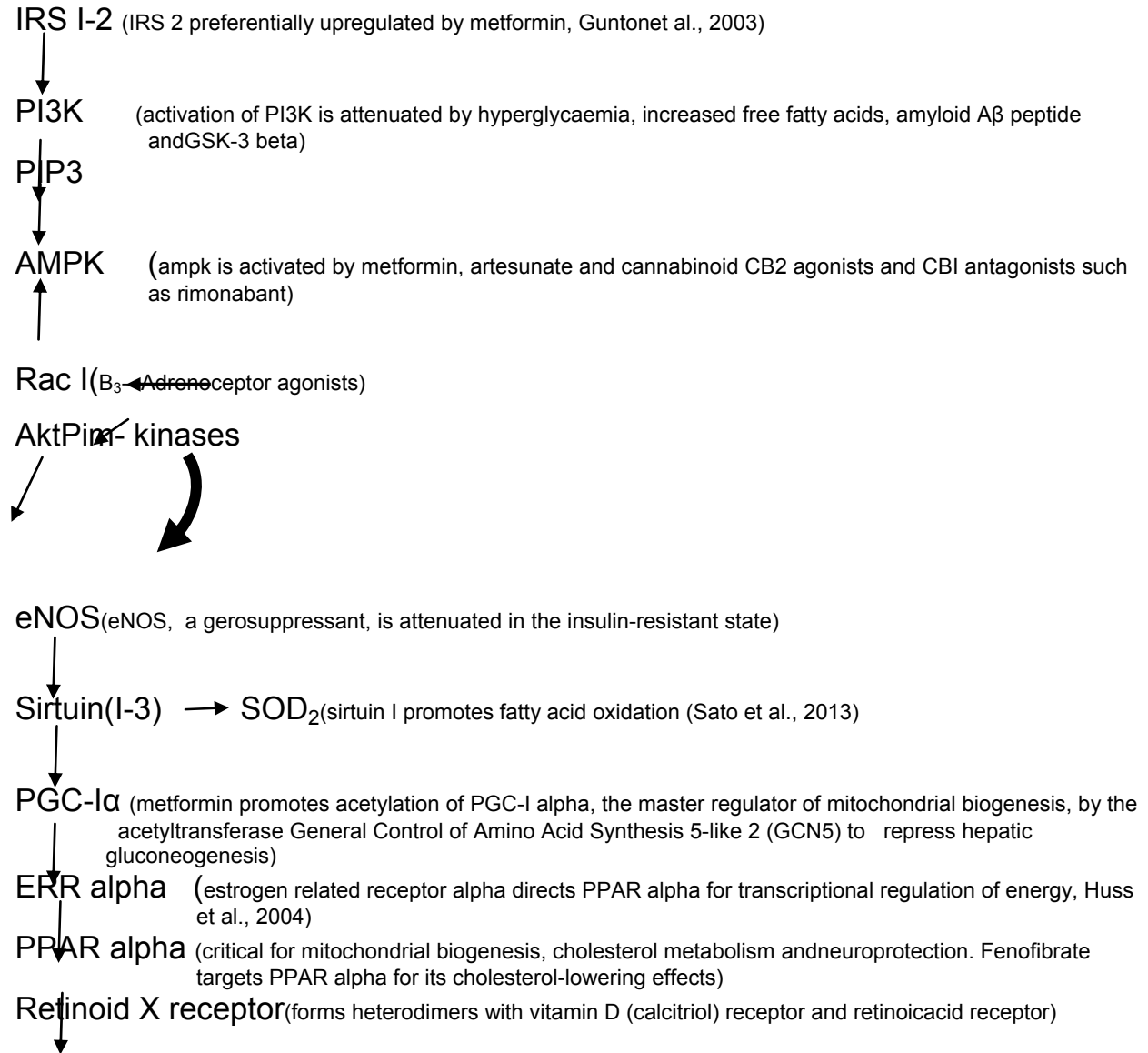


Figure II: Metformin, artesunate and cannabinoids increase PPAR alpha signaling important for mitochondrial function and lipid oxidation, thereby attenuating the effects of ROS/MMPs/GSK-3 beta signaling which poses risk for atherosclerosis, coronary artery disease, stroke and seizure susceptibility. IRS: insulin receptor substrate; PI3K: phosphoinositide 3-kinase; PIP3: phosphatidylinositol 3,4,5-triphosphate; AMPK: 5' adenosine monophosphate activated protein kinase; Rac I: GTPase; Akt: protein kinase B; Pim-kinase: pro-viral insertion site for moloney leukaemia virus; eNOS: endothelial nitric oxide synthase; Sirtuin I: NAD-dependent deacetylase silent information regulator; PGC-I alpha: peroxisome proliferator activated receptor gamma-coactivator I alpha; ERR alpha: estrogen related receptor alpha; PPAR alpha: peroxisome proliferator activated receptor alpha

drug, fenofibrate. Recently, it became clearer that it is the cannabinoid CB2 receptor that upregulates protein kinase B, -endothelial nitric oxide, -silent information regulator-I, -peroxisome proliferator-activated receptor gamma-

coactivator-I alpha, -estrogen-related receptor-alpha, -peroxisome proliferator activated receptor-alpha signalling (Akt-eNOS-Sirt I-PGC-I alpha-ERR alpha-PPAR alpha signaling) (Figure II) to increase lipid

oxidation by upregulating mitochondrial biogenesis and downregulating inflammatory mediators mediated by reactive oxygen species-matrix metalloproteinases-glycogen synthase kinase-3 β (ROS-MMPs-GSK-3 β) signaling (Zheng et al., 2013; Tedesco et al., 2010; Crespillo et al., 2011; Bermudez-Silva et al., 2007; 2006; Huss et al., 2004). Importantly, Cota et al. (2003) had shown that the endocannabinoids affect energy balance via central orexigenic drive and peripheral lipogenesis in mice. Weiss et al. (2006) demonstrated in non-obese mice that cannabidiol, which may activate CB2 receptors to form heteromers with serotonin 5HT(1A) receptors (Pazos et al., 2013), lowers incidence of diabetes.

Cannabinoid CBI inhibition has been demonstrated not to affect Akt or extracellular signal-regulated kinase activation by cannabinoids (Samson et al., 2003). Nevertheless, Sun et al. (2007) showed that the high affinity synthetic CBI/2 cannabinoid agonist WIN 55,212-2 binds to PPAR alpha equipotently with the PPAR alpha agonist, fenofibrate and increases PPAR alpha-mediated gene transcription which is also important for cognition.

Metformin has been reported to prevent progression of impaired fasting plasma glucose, decrease BMI (Oriaifo et al., 2013) and to increase mitochondrial biogenesis (Martin-Montalvo et al., 2013).

Artesunate has been reported to be a calorie-restriction-mimetic and to increase mitochondrial biogenesis via upregulation of Akt-eNO signalling, thus upregulating the global anti-oxidant network (Wang et al., 2015). We have demonstrated in our laboratory that chronic artesunate lowers blood sugar and decrease body weight in mice.

The effects of mitochondrial dysfunction

Diabetes mellitus and a hyperactive mTOR signalling increase generation of ROS which may cause genetic mutation by damaging DNA and mitochondria (Potter et al., 2010; Robertson et al., 2004). The molecular mechanisms involved in the premature senescence associated with hyperglycaemia include oxidative stress and decreased mitochondrial repair capacity.

Mitochondrial dysfunction as a result of defective endothelial nitric oxide signalling (Sartoret et al., 1999) is a hall-mark of the high cardiovascular risk in the metabolic syndrome (Nisoliet al., 2007; 2003; Patel et al., 2000; Jobgenet al., 2006); epilepsy (Waldbaum and Patel, 2010); Alzheimer's disease (Moreira et al., 2010; Aulston et al., 2013); decreased threshold to MPTP-induced seizures and cerebral ischaemia (Chen et al., 2011). Endothelial nitric oxide *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 (Ceriello et al., 2004; Hink et al., 2001; O'Sullivan et al., 2014). Thus, endothelial nitric oxide through boosting anti-oxidant mechanisms and decreasing brain excitability may occupy a central place in cardiometabolic and neuropsychiatric disorders (Patel et al., 2000; Murashima et al., 2000; Ferraro and Sardo, 2004; Wang et al., 2014). It decreases lipid peroxidation while upregulating glutathione production and serotonin release.

Metformin, artesunate and cannabinoid CB2 receptor agonists enhance mitochondrial biogenesis

Metformin, artesunate and cannabinoid CB2 receptor agonists/CB1 inverse agonists increase proteins involved in enhancing mitochondrial function (Figure II) (which has 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; 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 II).

Mitochondrial dysfunction is the basis of the neurotrophic and mitochondrial hypotheses of mood disorders (Hroudova et al., 2013) (Figure I). Energy saved in ATP is used in synaptic ion homeostasis and phosphorylation reactions. ATP is essential for the excitability and survival of neurons. Oxidative phosphorylation (OXPHOS) is involved in synaptic signalling and is related to changes of neuronal structure and function. Therefore, mitochondria are involved in neurotransmitter exocytosis, in recovery, and in ion homeostasis, and there is increased accumulation of mitochondria in the growth cones of presynaptic nerve terminals. Oxidative phosphorylation enzymes and monoamine oxidase (MAO) are key mitochondrial enzymes studied in molecular psychiatry (Hroudova et al., 2013).

Metformin, artesunate and cannabinoid CB2 receptor agonists/CBI inverse agonists upregulate AMPK activation

The serine/threonine kinase, 5'-adenosine mono phosphate 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), artesunate (Wang et al., 2015; Tan et al., 2014) 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 CBI receptors, enhances mitochondrial biogenesis (Tedesco et al., 2008).

High-fat diet has variable effects on cannabinoid CB2/CBI receptor signalling

Obesity is a major pandemic of the 21st century and there is decreased eNOS in obesity with increase of iNOS which promotes insulin resistance (Sansbury and Hill, 2014). High-fat diet promotes mitochondrial dysfunction (Anderson et al., 2009) and enhances cannabinoid CB1 signaling which contributes to increased lipogenesis (Osei-Hyiaman et al., 2005) while decreasing cannabinoid CB2 receptor and PPAR alpha gene transcription (Crespillo et al., 2011). As shown by the authors, high-fat diet also upregulates monoglyceride lipase (MAGL).

Cannabinoids and metformin enhance pancreatic beta-cell neogenesis

Cannabinoids such as 2-oleoyl glycerol acting via G-protein coupled receptors-119 (GPR 119) (Hansen et al., 2011) and metformin (Verspohlet et al., 2012) or artesunate acting through nitric oxide (Vasilijevic et al., 2007) upregulate glucagon-like peptide-1 (GLP-1), the incretin of major importance, which enhances pancreatic beta-cell neogenesis, lowers glucose levels and which does not cause weight gain unlike DPP-4 inhibitors such as vildagliptin.

Cannabinoids, metformin and artesunate enhance cognition

Cannabinoids, metformin and artesunate stand to enhance cognition through their anti-oxidant effects (Hettich et al., 2014; Martincet et al., 2014; Wanget al., 2015;) to which PI3K-eNOS signalling contributes. Food restriction by these agents reduces brain damage and improves behavioural outcomes following excitotoxic and metabolic insults (Bruce-Keller et al., 1999). Dietary restriction attenuates the neuronal loss, induction of hemoxygenase-1 and blood-brain-barrier (BBB) breakdown induced by impaired oxidative metabolism (Calingasan and Gibson, 2000). Cannabinoid CB1/CB2 receptors share 68% homology (similar amino-acids) in

their transmembrane domains (Galie'gue et al., 1995; Lutz, 2002) and both are important for neuroprotection (Sun et al., 2007). For example, in multiple sclerosis, a disease that may be related to obesity (Hedstrom et al., 2014; Procaccini et al., 2011), CBI/2-mediated epigenetic regulation of mitogen-activated protein kinase phosphatase-1 expression may be protective (Eljaschewit et al., 2006). In vitro, anandamide prevents A β -induced neurotoxicity through CBI-mediated activation of the mitogen-activated protein kinase pathway (Milton, 2002) and decreases iNO release implicated in the neurotoxic effects of A β peptide (Waksman et al., 1999). CBI-positive neurons are greatly reduced in areas of microglial activation in Alzheimer's disease (Ramirez et al., 2005) and both CBI and CB2 agonists have been reported to be neuroprotective.

Among the more than 100 cannabinoids present in marijuana, only tetrahydrocannabinol (THC) which signals through CBI receptors is psychoactive and this is a disadvantage. It is observed that THC may actually be more potent agonist at GPR 18 receptor than at CB1 or CB2 receptors, initiating directed microglial activation in the CNS through activation of GPR 18 or N-arachidonoyl glycine receptor (Wikipedia.org; McHugh et al., 2011). Ajulemic acid, a metabolite of THC, activates only CB2 receptors (Rhee et al., 1997). THC may also signal through the transient receptor potential vanilloid-1 (TRPV-1) to exhibit vasodilator effects through calcitonin-gene related peptide (CRRP) (Pacher et al., 2006). However, CB2 specific compounds have considerable therapeutic appeal over CBI compounds as they are devoid of psychoactive effects that plagues CBI-directed therapies (Ashton and Glass, 2007).

Tolerance to cannabinoid CBI receptors in chronic daily cannabis users

There may be reversible and regionally selective downregulation of brain cannabinoid CBI receptors in chronic daily cannabis smokers (Hirvonen et al., 2012) and this may lead to increase signalling by CB2 receptors.

Cannabinoid CB2 receptor agonists ameliorates Alzheimer's disease-like phenotype (Aso et al., 2013) and shows metformin-like effects (Oriaifo et al., 2015) in downregulating proinflammatory cytokines, inhibiting glycogen synthase kinase-3 β , lowering tau hyperphosphorylation and enhancing, like artesunate, SOD2.

Metformin and cannabinoids promote neurogenesis

Metformin's and artesunate's calorie restriction-mimetic

effects upregulate neurogenesis (Lambaet al., 2005; Potts et al., 2012). In the same vein, endocannabinoids and cannabinoid CB2 receptor agonists promote neural progenitor cell proliferation (Aguadoet al., 2005; Palazuelos et al., 2011).

Cannabinoids, metformin and artesunate in epilepsy

Work in our laboratory has demonstrated significantly that chronic administration of metformin and artesunate possess anti-epileptogenic and anti-epileptic effects corroborating previous work in this area (Stone et al., 2014; Zhao et al., 2014; Sanjana et al., 2012). These actions may be explained at the molecular level by their effects in upregulating PIP3-Akt-eNOS-PGC-1 α signalling since all the factors in this pathway attenuate seizures by inhibiting ROS-MMPs-GSK-3 β signalling (Murashima et al., 2000; Sanjana et al., 2012; Wilczynski et al., 2008; Vezzani et al., 2011). Molecular mechanisms that decrease threshold for seizures converge on MMPs and GSK-3 β (Ceriello et al., 2004; Mizoguchi and Yamada, 2013). Additionally, CB2 agonists, metformin and artesunate which activate AMPK (Kuramoto et al., 2007) and increase nitric oxide-cGMP signalling potentiates GABA which is anti-epileptogenic (Wang et al., 2006; Zeng and Phang, 2011). Moreover, activation of CB2 receptors by upregulating BBB function (Ramirez et al., 2012) may help decrease pharmacoresistance in epilepsy. Cannabidiol-enriched cannabis may be advantageous in pediatric treatment-resistant epilepsy (Porter and Jacobson, 2013).

Chronic marijuana use is protective against seizures (Ng et al., 1990) and anandamide dose-dependently inhibits electroshock-induced seizures in rats (Wallace et al., 2002). "On-demand" activation of CBI receptors may be protective against seizures (Lutz, 2004; Marsicano et al., 2003; Khaspekova et al., 2004). Seizure-induced increase of intra-cellular calcium, a hallmark of epilepsy (Raza et al., 2001), triggers the release of anandamide which activates CBI receptors in glutamatergic neurons in the hippocampus and cerebral cortex.

Cannabinoid CB2 agonists are protective in a hyperdopaminergic state

There is lack of morphine-induced dopamine release in the nucleus accumbens of CBI knock-out mice and ablation of CBI receptors prevents opioid effects. Cannabinoid CB2 receptor agonists decrease ventral tegmental area dopamine neuronal activity and modulate dopamine-related behaviour (Zhang et al., 2014). So, CB2 agonists such as the trans-isomer of beta-caryophyllene (Gertschet et al., 2010) may help prevent

abnormal behaviours in a hyperdopaminergic state. Such abnormal behaviours may include bipolar disorder, an age-related disease (Rizzo et al., 2014), which has overlapping aetiopathogenetic mechanisms with epilepsy (Kanner et al., 2014).

Cannabinoids, metformin and artesunate possess anti-depressant-like effects

There is a regulatory role of the cannabinoid CB2 receptor in stress-induced inflammation (Zoppi et al., 2014) and in upregulating beta-endorphin release (Su et al., 2011) while the cannabinoid CBI receptor inverse agonist AM 251 possesses anti-depressant-like effects in mice (Shearman et al., 2003). Dysfunction of mitochondrial metabolism may be cause or effect of mood disorders (Tobe, 2013; Hroudova et al., 2013; Quiroz et al., 2008) and agents such as the CBI receptor antagonist/inverse agonist, rimonabant (Tedesco et al., 2008), the anti-diabetic, metformin (Guo et al., 2014), the sesquiterpenetrioxone lactone, artesunate and the cannabinoid CB2 receptor agonists, such as cannabidiol, which upregulate mitochondrial biogenesis and serotonin 5-HT_{1A} receptor signalling (Pazos et al., 2013) exhibit anti-depressant(-like) effects. In our laboratory, we have also demonstrated the anti-depressant effects of chronic metformin and artesunate administrations using the forced swim test in mice.

Cannabinoid CB2 receptor agonists, metformin and artesunate exhibit Akt-dependent cardioprotection

Protein kinase B or Akt signals to eNOS directly to transiently phosphorylate eNOS at serine 1177 or indirectly through Pim-kinase (upregulated by metformin (Leclerc et al., 2013) to maintain a sustained phosphorylation of eNOS at serine 633 (Fig. II) necessary for mitochondrial integrity preservation in the cardiomyocyte and enhanced cardioprotection (Chen et al., 2013; Sussman, 2009; Pillai et al., 2014). In diabetes mellitus, there is deficient activation of Akt-eNOS signalling by insulin. AMPK activation by metformin or artesunate (Wang et al., 2015; Janneh et al., 2014) or the use of the novel protein kinase C isoform (protein kinase D) may restore Akt activation in insulin-resistant cardiomyocytes (Bertrand et al., 2006) thus improving left ventricular function and survival in heart failure (Gundewar et al., 2009; Viollet et al., 2010). The cannabinoid CB2 receptor axis through AMPK activation is also cardioprotective (Duerret et al., 2014) though it has been reported that a CBI/CB2 dual agonist with limited brain penetration, CB-13, was more efficacious (Liu et al., 2014). It is noted, though, that it has been reported that

pharmacologic inhibition of CBI receptors may offer cardioprotection (Mukhopadhyay et al., 2008). Both cannabinoid CB2 agonists (Wang et al., 2014) and metformin (Albiero et al., 2014) may activate cardiac progenitor cells.

Hypertension and atherosclerosis

Metformin and calorie restriction restore leptin sensitivity in rodents with high-fat induced insulin resistance (Kim et al., 2006) to prevent actions that are potentially atherogenic, thrombotic and angiogenic (Perez et al., 2004). Metformin also increases endothelial progenitor cells that are reduced in diabetic mellitus (Liao et al., 2010; Fadiniet al., 2005). It has been reported that the hypotension/bradycardia effects of exogenous anandamide are mediated via cannabinoid CBI receptors (Vargaet al., 1995; Lake et al., 1997). Cannabinoid CB2 receptor agonists are reported to be protective in atherosclerosis probably via upregulation of endothelial nitric oxide (Roth, 2005; Steffens et al., 2005) and adiponectin.

Cannabinoids, metformin and artesunate increase CD4+T-cell/CD8+T-cell ratio and CD4+Foxp3+Tregs

There is a potential role of regulatory T-cells in reversing obesity-linked insulin resistance and diabetic nephropathy (Eller et al., 2011) for obesity results in adipose T-reg depletion (Deiuliiset al., 2011). Fasting-induced hypoleptinaemia expands functional regulatory CD4+Foxp3+Tregs which improves insulin sensitivity and diabetic nephropathy (Liu et al., 2012). Fasting is beneficial in autoimmune diseases and the increased leptin signalling in obesity, type 2 diabetes mellitus or secondary to oestradiol or recombinant FSH inhibits CD4+CD25+Foxp3+Treg important for immune tolerance (Geber et al., 2012). Deacetylase inhibition or AMPK activation by metformin or valproate or artesunate increases regulatory T-cell function to decrease autoimmune diseases (Saouatet al., 2009; Feuereret al., 2009; Li et al., 2013). These T-reg which are CD4+CD25+Fox3+Tregs are reduced in insulin resistance and in immunologic reproductive failure (Winger and Reed, 2011). Metformin increases Tmemory fate of CD8+T-cells and improves the efficacy of cancer vaccine (Pearce et al., 2009), restoring fatty acid oxidation and CD8+Tmem cell generation (Finlay and Cantrell, 2011). Metformin or the cannabinoid receptor agonist, Gpla, increases the ratio of CD4+/CD8+ T-cells (Feuereret al., 2009; Gorantiaet al., 2010) and enhances Th2 over Th1 dominance (Weiss et al., 2006). This increased ratio may

be beneficial in HIV-I-associated neurocognitive deficit (HAND)

CONCLUSION

Review show that metformin, artesunate and cannabinoids (especially cannabinoid CB2 receptor agonists with non-psychoactive effects) attenuate factors of the metabolic syndrome and also show benefit in neuropsychiatric and immune-based illnesses. Present evidence shows that their effects converge on mitochondrial function and seems to indicate that there isa link between cardiometabolic disorders such as diabetes mellitus and neuropsychiatric disorders such as epilepsy and depression.

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