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Review Article

Brain insulin resistance: A treatment target for cognitive impairment and anhedonia in depression

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) and Major Depressive Disorder (MDD) are leading causes of disability worldwide. Indeed, both are costly and burdensome diseases at both individual and socio-economic levels. Notably, there are similar pathophysiological elements, which might explain the overlap in phenotypic symptoms and the high rate of comorbidity. Brain insulin resistance is a shared metabolic abnormality amongst many individuals with T2DM and MDD. Patients with either or both diseases often exhibit disturbances in cognition and mood, as well as the presence of anhedonia-like symptoms. However, individuals with T2DM with high glycemic control have reduced cognitive and depressive symptom burden. Based on this evidence, it is possible that repurposing therapies approved for treating insulin resistance may be useful in treating cognitive and anhedonia symptoms in depression. The objective of this review is to discuss the relationship between brain insulin resistance and depression, as well as possible disease modifying therapeutic agents targeting insulin signalling.

1. Introduction

Mental illness is a complex pathophysiological disease with heterogenous etiology. Convergent evidence suggests mental illness may be caused by a disruption in normal insulin signalling in the brain. Individuals with Type 2 Diabetes Mellitus (T2DM), a disease characterized by impaired insulin sensitivity, have an increased risk of depression (Cannon et al., 2018). Epidemiological evidence suggests that 1 in 4 patients with T2DM suffers from clinical depression (World Health Organization, 2018). Individuals with metabolic risk factors for insulin resistance including high cholesterol, obesity, older age, and hypertension, also have a greater risk of suffering from depression (Gangwisch et al., 2015). In addition, clinical depression has been demonstrated to significantly increase the risk of developing T2DM and/or other metabolic complications such as peripheral insulin resistance, metabolic syndrome, and vascular disease (Cannon et al., 2018; Semenkovich et al., 2015; Ryan et al., 2012). Thus, there is a bidirectional relationship between insulin resistance and depression, as evidenced by their high rate of comorbidity.

Previously, the brain was considered an “insulin-insensitive organ” because, unlike in the periphery, insulin is not needed for glucose transport into the central nervous system (CNS) (Blázquez et al., 2014). However, insulin is a critically important neuropeptide needed for cognitive functioning as well as other neurotrophic, neuromodulatory and neuroprotective processes (Blázquez et al., 2014; Gray et al., 2014). Some research suggests that peripheral insulin resistance can metastasize to the brain leading to brain insulin resistance; while other studies suggest brain insulin resistance may manifest independently as part of underlying brain pathology in mental illness (Kamal Sachdeva et al., 2018; Sripetchwandee et al., 2018; McIntyre et al., 2007; Talbot et al., 2012). In either scenario, both central and peripheral insulin resistance can have detrimental effects on the brain, such as a decline in cognition and mood, as well as the presence of anhedonia-like symptoms (Sripetchwandee et al., 2018).

Current treatment for depression is symptom-suppressing as opposed to disease-modifying, underscoring the need for novel treatment interventions. The most common type of intervention for depression is pharmacotherapy (i.e., antidepressant medication, mood stabilizers), which does not always alleviate symptoms. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), 50–66% of patients with

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major depressive disorder (MDD) do not achieve remission from the first antidepressant treatment trial. Moreover, amongst only 30% of treatment responders remain in remission (Al-Harbi, 2012; National Institute of Mental Health, 2018). Despite the remission of their primary symptoms, patients suffering from MDD still experience residual symptoms including cognitive deficits and apathy that ultimately affect their fundamental quality of life (Israel and The, 2010). Cognitive impairment can also predict the onset of MDD (Park et al., 2018). The Research Domain Criteria (RDoC) has established that cognitive impairment is a core domain of MDD diagnosis and that brain insulin resistance is a commonality in both mood disorders and cognitive disorders (National Institute of Mental Health, 2018). Conventional pharmacological interventions include agents that target the serotonin and/or dopamine system, and these may not be targeting underlying pathoetiological mechanisms such as insulin signalling which could have the potential to modify disease progression. Cognitive behavioural therapy (CBT) has shown to be very successful in reducing depressive symptoms and may in part be working through the enhancement of insulin sensitivity (Shomaker et al., 2017). Similarly, exercise has shown to reduce the incidence of MDD, mitigate depressive symptoms and anhedonia, as well as improve insulin signalling (Harvey et al., 2018; Toups et al., 2017; Cockcroft et al., 2017; Hansen et al., 2017). This review will evaluate the commonalities between brain insulin resistance, cognition and anhedonia as well as illustrate that brain insulin signalling is a compelling therapeutic target to treat the cognitive and metabolic abnormalities in depression.

2. Brain insulin

2.1. Location, origin & receptors

Insulin was discovered in the rodent brain in 1978 by Havrankova et al., at concentrations 25 times greater in brain tissue than in the plasma (Havrankova et al., 1978; Havrankova et al., 1979). Brain insulin is regulated independent of peripheral insulin activity and is found throughout the brain, but at higher concentrations in the hypothalamus, hippocampus and cortex than in the plasma (Sripetchwandee et al., 2018). Insulin derivatives have been identified in fetal and neonatal mammalians prior to pancreatic development, suggesting insulin may be synthesized from cells in the brain; however this remains controversial (Blázquez et al., 2014). Insulin can also cross the blood brain barrier (BBB) via a saturable transporter, suggesting insulin in the brain may originate from both brain and pancreatic sources (Banks et al., 2012; Butterfield et al., 2014; Werner and LeRoith, 2014; Banks, 2004). Insulin transporters are located on the human cerebrovascular endothelial cells (HCECs) of the BBB and transportation across the BBB is region-dependent: higher insulin permeability is observed in the pons, medulla and hypothalamus, and lower permeability in the occipital lobe and thalamus (Baura et al., 1996). It is estimated that < 1% of peripheral insulin administered intravenously reaches the CNS, but transportation can be modulated by physiological factors, such as amino acids, hormones, aging and disease states such as T2DM, obesity and Alzheimer's Disease (AD) (Banks et al., 2012). The uptake of insulin across the BBB also affects efflux transporters, specifically P-glycoprotein expression to increase, suggesting insulin uptake may improve the integrity of the BBB by further protecting it from toxins (Liu et al., 2009).

There are two isoforms of the insulin receptor (IR) generated by alternate splicing of exon 11 of a single gene, producing IR-A and IR-B. In humans, the longer of the two isoforms, IR-B is found in the periphery, mainly the liver, adipose tissue and skeletal muscle, while IR-A is found solely in the brain (Blázquez et al., 2014; Moller et al., 1989). These receptors are not only structurally different in size, shape and level of glycosylation, but they also differ in mechanisms for activation and regulation (i.e., response to excess insulin, IR-B is downregulated in the periphery, but IR-A is not affected in the brain) (Blázquez et al., 2014; Belfiore et al., 2017). IR-A is specifically expressed on neurons in the brain which mediate a variety of nonmetabolic effects, while some IR-B receptors are expressed on astrocytes mediating metabolic processes in the brain. An unbalanced ratio of IR-A and IR-B has shown to be associated with insulin resistance (Belfiore et al., 2017). Those with a higher expression of IR-A and in a diabetic or pre-diabetic state of peripheral hyperinsulinism have non-metabolic IR actions favoured and IR-B metabolic processes reduced, which may exacerbate metabolic dysfunction in the brain (Belfiore et al., 2017). Interestingly, patients with abnormal ratios of IR-A to IR-B have this ratio corrected approximately 17 months after undergoing bariatric surgery, suggesting improved insulin sensitivity improves IR isoform expression (Besic et al., 2015). Therefore, regulation and monitoring IR expression in the brain is critical in understanding insulin signalling.

Insulin receptors are found throughout the brain (both neurons and glia) with the highest expression found in regions regulating autonomic activity, appetite, and olfaction as well as emotional and cognitive function (Havrankova et al., 1978; Werther et al., 1987; Marks et al., 1990). This includes the hippocampus, olfactory bulb, amygdala, septum, cerebellum, hypothalamus and cerebral cortex (McIntyre et al., 2007). Given the olfactory bulb has one of the highest levels of IR in the brain it is often studied for therapeutic purposes as intranasal administration of insulin bypasses the BBB (Werner and LeRoith, 2014; Marks et al., 2009). Insulin receptors are often co-localized with glucose transporters in the brain, and although they independently modulate glucose utilization, their co-localization suggests a synergistic effect with insulin and glucose in regulating brain processes (Sripetchwandee et al., 2014).

2.2. Brain insulin signalling

Contrary to peripheral IR signalling, insulin's ability to affect glucose transport is region-dependent. While the predominate brain glucose transporters (GLUT) are insulin-insensitive, mainly GLUT-1 and GLUT-3 there are several regions with insulin-sensitive GLUT-4 such as the hippocampus and some cortical areas (Bingham et al., 2002; Benomar et al., 2006). During hippocampal-dependent cognitive tasks, insulin stimulate the translocation of GLUT-4 to the plasma membrane, increasing brain glucose utilization (Pearson-Leary et al., 2018). This suggests insulin signalling may play a tandem role with glucose utilization in memory and learning. Similar to the periphery, chronic exposure of insulin has shown to downregulate GLUT-4 translocation in these brain areas, which may in turn affect insulin-sensitive hippocampal-mediated cognition (Benomar et al., 2006; Pearson-Leary et al., 2018). It is unclear if other brain regions with GLUT-4 expression aside from the hippocampus are activated by an influx of insulin yet or if they impact cognitive processes (Sripetchwandee et al., 2018).

The effects of insulin in the brain are mediated by two main pathways: the phosphoinositide-3 kinase (PI3K)/Akt and the Ras/mitogen activated kinase (MAPK) signalling cascades (Banks et al., 2012). Binding of insulin to IR initiates the phosphorylation of tyrosine residues on insulin receptor substrate (IRS), which then activates a cascade of downstream signalling pathways through various activated kinases (Banks et al., 2012). Although the majority of studies suggest brain insulin is strongly associated with cognitive function, there are numerous IR signalling effects from feeding behaviour, weight management and nutrient homeostasis to memory, cognition and reproduction (Blázquez et al., 2014). These effects can be grouped into neurotrophic, neuromodulatory and neuroprotective processes.

2.3. Neurotrophic processes of brain insulin

Neurotrophins are defined as brain proteins involved in the growth, development, survival and function of neurons (Hodgetts and Harvey, 2017). Insulin binding to IR induces a cascade of various neurotrophic processes, including synaptogenesis, dendritic spine formation, and

neurogenesis (Blázquez et al., 2014). For example, through activation of the PI3K/ mammalian target of rapamycin (mTOR) pathway, insulin increases the protein expression of dendritic scaffolding protein post-synaptic density 95 (PSD-95) in the hippocampal CA1 neurons. PSD-95 is necessary for the survival and reformation of dendritic spines and is impaired in models of depression and chronic stress (Qiao et al., 2016; Berry and Nedivi, 2017). IR binding also activates IRS-2 which stimulates neurite growth factor (NGF), a neurotrophic factor needed for brain neurite formation (Blázquez et al., 2014). Given insulin's importance in modulating synaptic function and neurite growth, it is also critical in neurodevelopment. IR signalling has shown to be involved in the proliferation, development and maturation of neurons during brain development (Wozniak et al., 1993; Xu et al., 2004). There is a high expression of IR subcortically and in the brainstem during cell differentiation (Wozniak et al., 1993). Evidence of insulin-deficiency, as seen in untreated early-onset type 1 diabetes mellitus (T1DM) in developing countries, has shown to lead to poor brain development, as well as severe cognitive impairment in youth (Yau et al., 2000). Even children exposed to gestational diabetes mellitus have an increased risk of impairments in neurodevelopment and cognition (Torres-Espinola et al., 2015; Van Dam et al., 2018). Thus, insulin is a powerful neurotrophin involved in a variety of neuronal processes.

Two other hormones with a similar sequence to insulin, specifically insulin-like growth factor (IGF) I and IGF-II, also exhibit neurotrophic properties. It has been proposed IGF-I works synergistically with brain derived neurotrophic factor (BDNF) to activate neurotrophic processes in the hippocampus that promote cell survival and plasticity for learning and memory (Paslakis et al., 2012). IGF-I also directly stimulates neurogenesis, suggesting potential anti-depressant enhancing capabilities. Similarly, IGF-II works alongside insulin and IGF-I in a binding protein system that is vital in memory and consolidation (Werner and LeRoith, 2014).

2.4. Neuromodulatory processes of brain insulin

Insulin has a significant endocrine role in modulating energy expenditure as well as feeding and reward behaviours (Plum et al., 2005; Scherer and Buettner, 2011). At a molecular level, insulin stimulates hypothalamic anorexigenic signalling that inhibits food intake while inhibition of insulin promotes orexigenic effects, promoting weight gain and increased feeding behaviour (Plum et al., 2005; Scherer and Buettner, 2011). Unlike in the periphery, where insulin and glucagon have opposing roles on blood glucose, they work in tandem in the brain to lower food intake, manage body weight and maintain glucose homeostasis (Filippi et al., 2013). In animal models with dysfunctional neuronal IRs, food intake increases and administration of insulin to the ventral tegmental area (VTA) or arcuate hypothalamic nucleus decreases food intake (Brüning et al., 2000; Bruijnzeel et al., 2011). Insulin in the VTA also decreases brain reward functioning, suggesting insulin plays a vital role in modulating behaviour and emotional cognition (Bruijnzeel et al., 2011).

The high prevalence of IR on the hippocampus highlights insulin's role in learning, memory, and synaptic plasticity. Insulin mediates long-term potentiation (LTP) by modulating AMPA receptor expression and thus glutamatergic signalling at the post-synaptic membrane – a process necessary for learning and memory (Sripetchwandee et al., 2018). In the cerebellum, insulin stimulates GABAergic inhibitory activity which is also thought to be involved in the regulation of feeding behaviour (Kovacs and Hajnal, 2009). Administering an IR inhibitor abolishes this insulin-dependent GABAergic inhibitory effect (Kovacs and Hajnal, 2009). Interestingly, the hippocampus and cerebellum are major regions where insulin signalling is impaired in Alzheimer's disease (AD), suggesting a potential relationship between brain insulin resistance, neurodegeneration and cognitive decline (Talbot et al., 2012). Lastly, depending on the concentration of the hormone, insulin also modulates norepinephrine, catecholamine and dopamine, reuptake and turnover (Blázquez et al., 2014). Overall, insulin has complex neuromodulatory effects on the brain.

2.5. Neuroprotective processes of brain insulin

An important function of insulin in the CNS is neuronal cell survival (Werner and LeRoith, 2014). Insulin and insulin-sensitizing agents have been explored as potential therapeutic targets for stroke, neuronal injury and neurodegeneration, as insulin has shown to improve neuronal viability (de la Monte, 2012; Liu et al., 2014). Abnormalities in insulin signalling have been associated with tau hyperphosphorylation, amyloid-beta accumulation, synaptic disconnection and neuronal cell loss which are all hallmark neurodegenerative features in Alzheimer's disease (AD) (de la Monte, 2012). Insulin may be vital for inhibiting non-apoptotic autophagic cell death and slowing down the aging process (Wozniak et al., 1993; Valencia et al., 2017). Activation of IR-A leads to the phosphorylation and inhibition of glycogen synthase kinase (GSK)-3, thus inhibiting amyloid beta modulation, tau phosphorylation and production of inflammatory cytokines like interleukin (IL) 6. Inhibiting GSK-3 also increases the production of anti-inflammatory cytokines like IL-10 (Blázquez et al., 2014). If insulin signalling is reduced, GSK-3 remains active increasing tau hyperphosphorylation and inflammation, both of which can cause deleterious effects in the brain. Activated GSK-3 also reciprocally inhibits IR and IRS-1, which in turn leads to brain insulin resistance (Blázquez et al., 2014).

3. Brain insulin resistance

3.1. Mechanisms

Presently, the gold standard for measuring peripheral insulin sensitivity is using a euglycemic insulin clamp, however, measuring brain insulin poses greater challenges with reduced accessibility and no consensus on the definition or diagnostic characterization of brain insulin resistance (Ferrannini and Mari, 1998; Talbot, 2014). There is a lot of variation amongst studies in the biomarker used for evaluating brain insulin dysfunction from reduced phosphorylation of IRS-1, to mitochondrial changes to many other downstream signalling targets of insulin (Blázquez et al., 2014; Sripetchwandee et al., 2018; Talbot, 2014). However, understanding impairments in peripheral insulin signalling is important as it is associated with cognitive dysfunction, suggesting peripheral insulin resistance may metastasize to the brain (Kamal Sachdeva et al., 2018; Sripetchwandee et al., 2018; Filippi et al., 2017; Pathan et al., 2008).

In the periphery, insulin works alongside GLUT-4 to uptake glucose from the blood into muscle, adipose, and liver tissue (Lawrence et al., 1992). With peripheral insulin resistance, the pancreas overproduces insulin in response to elevated blood-glucose levels leading to hyperinsulinemia. Consequently, this impairs energy homeostasis and has shown to increase lipolysis (i.e., release of free fatty acids from adipocytes), release of pro-inflammatory cytokines, production of reactive oxygen species (ROS) and an increased production of triglycerides through modifying gene expression and protein synthesis (Ryan et al., 2012; Plum et al., 2005; Lawrence et al., 1992; Jeong et al., 2018). Indeed, it may be that the metabolic changes in the periphery lead to neuroinflammation and brain insulin resistance, which in turn cause impairments in neuronal signalling and synaptic plasticity (Kamal Sachdeva et al., 2018). In a preclinical study by Sachdeva et al., peripheral insulin resistance, induced by a high fructose diet for 7 weeks, leads to lasting symptoms of cognitive dysfunction starting at week 20 (Kamal Sachdeva et al., 2018). Other pre-clinical studies have shown a timeline from peripheral to brain insulin resistance ranging from 3 days to several weeks (Sripetchwandee et al., 2018). This research suggests that peripheral metabolic changes can induce impairments in CNS functioning.

Emerging evidence suggests that brain insulin resistance may

develop through the phosphorylation of specific serine residues on IRS-1/2 by the c-Jun N-terminal kinase (JNK1) and other kinases which inhibit insulin-stimulated phosphorylation and downstream pathway activation (Blázquez et al., 2014; Aguirre et al., 2002). However, a consensus on the definition of brain insulin resistance is needed as biological markers vary from study to study. An outcome that has consistently been evaluated amongst brain insulin resistance studies is impairment in cognition and reward.

3.2. Brain insulin resistance & reward

Insulin modulates dopaminergic mesolimbic pathways, responsible for motivation and reward (Kullmann et al., 2016). Impairments in these insulin-dependent homeostatic mechanisms can decrease dopamine signalling. Particularly in the dopaminergic neurons of the ventral striatum, abnormalities in insulin signalling have been related to depressive symptoms, while insulin resistance in the amygdala has shown increased reward-seeking behaviour (Kullmann et al., 2016; Areias and Prada, 2015). Insulin resistant individuals with depression have shown to have greater levels of anhedonia and more food seeking behaviour than those with normal insulin signalling and depression (Singh et al., 2018). A magnetic resonance spectroscopy study with 50 non-medicated individuals with depression suggests this may be in part due to increased glutamate in brain regions subserving reward and motivation (Haroon et al., 2016).

Therefore, insulin sensitivity may be associated with changes in glutamate signalling and reward processing in depression and could subsequently lead to obesity, exasperating metabolic dysfunction (Jantaratnotai et al., 2017). A recent meta-analysis suggests that depressed individuals have a 70% increased risk of obesity, and those who are obese have a 40% increased risk of depression, suggesting there is convergence of depression, insulin resistance and reward-seeking behaviour (Mannan et al., 2016).

Cortical thickness has shown to vary in depressed individuals based on insulin sensitivity. For depressed individuals with low fasting insulin levels, greater depression severity positively correlates with thickness of the anterior cingulate cortex (ACC), whereas in insulin resistant individuals' cortical thickness is negatively associated with depression severity. Therefore, there is reduced gray matter volume with greater depressed symptoms for individuals with insulin resistance (Singh et al., 2018). Given the ACC is involved in emotional processing and decision making, changes in insulin signalling may lead to reduced ACC functioning and subsequently anhedonia in depressed individuals. A similar finding was seen in the hippocampus, showing that individuals with insulin resistance had a negative correlation between hippocampal volume and depressive symptoms, whereas those with low fasting insulin levels had a positive correlation (Talbot, 2014). A reduction in hippocampal volume may explain why cognitive impairments in learning and memory are observed in insulin resistant depressed individuals.

3.3. Brain insulin resistance & cognition

There is an increased risk for cognitive impairment in those who have brain insulin resistance (i.e., MDD, T2DM, AD) (Blázquez et al., 2014; Sripetchwandee et al., 2018; McIntyre et al., 2007; Talbot et al., 2012; Neth and Craft, 2017; Mansur et al., 2018). Insulin's neurotrophic, neuromodulatory and neuroprotective properties (as explained above) are likely responsible for the relationship between insulin signalling and cognition. A recent meta-analysis suggests there is a strong correlation between glycemic control and cognitive dysfunction, such that with metabolic abnormalities, there is an increased risk for cognitive impairment (Mansur et al., 2018). Individuals with T2DM present impairments across a multitude of cognitive domains, but those with tightly regulated insulin levels through medication are less likely to have cognitive dysfunction (Kawamura et al., 2012). A core domain disturbance in depression is cognitive dysfunction, but often is not a target of treatment (McIntyre et al., 2015). Brain insulin resistance also increases abdominal fat deposition, which has been associated with premature cognitive impairment (Ryan et al., 2012). Hyperinsulemina and obesity, both a result of insulin resistance and risk factors for insulin resistance, induce oxidative stress, neuroinflammation and increase pro-inflammatory cytokines (i.e., Tumor Necrosis Factor-alpha [TNF-], Interleukin-6 [IL-6], C-Reactive Protein [CRP]) while decreasing anti-inflammatory cytokines that alter hippocampal synaptic plasticity and spatial learning (Blázquez et al., 2014; Cetinkalp et al., 2014; Johnston et al., 2011). Pre-clinical models have demonstrated peripheral insulin resistance precedes cognitive impairment, suggesting peripheral insulin resistance can metastasize to the brain and lead to impaired brain functioning (Sripetchwandee et al., 2018). At the same time, pre-clinical models of hippocampus-specific insulin resistance have shown impairments in cognition independent of peripheral insulin signalling and glucose homeostasis (Grillo et al., 2015). This suggests changes in systemic insulin regulation may not be solely responsible for cognitive dysfunction and that brain insulin resistance may manifest independently. Changes in insulin signalling may also be region-dependent as IRs specifically in the hippocampus have been modified in those cognitively impaired with T2DM and AD (Biessels and Reagan, 2015). Interestingly, cognitive dysfunction in these models of insulin resistance have been reversed with anti-diabetic medication or treadmill exercise, both of which also improve insulin brain signalling, reduce oxidative stress and stimulate abdominal fat loss (Jeong et al., 2018).

4. Therapeutic targets

Based on the aforementioned findings, depression is both a metabolic and cognitive disorder. Novel treatments targeting insulin and it's signalling pathways show promise in treating cognitive and anhedonia symptoms in depressed individuals. As well, glycemic control may help with reducing depressive symptoms (Kivimaki et al., 2009; Winokur et al., 1988). Several treatment options have been explored including, intranasal insulin, intranasal IGF, and insulin sensitizing agents such peroxisome proliferator-activated receptor (PPAR) gamma agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors. Since depression has a bi-directional relationship with insulin sensitivity, treating the depression could also have potential metabolic benefits. For example, previous research has evaluated the use of psychotherapy interventions such as cognitive behavioural therapy (CBT), which not only improved depressive symptoms, but insulin resistance as well (Shomaker et al., 2017). The following studies examine the relationship between mood disorders and insulin resistance through various pharmacological and psychotherapeutic interventions. Despite differing methodology, all studies examined core symptoms of depression including, but not limited to, mood symptoms, cognitive disturbances, and anhedonia (See Table 1).

4.1. Intranasal insulin and IGF

Intranasal administration allows for a non-invasive, direct delivery of insulin to the brain, bypassing the BBB and thereby avoiding potential systemic side effects of lowering blood glucose levels (Born et al., 2002; Chapman et al., 2013). Intranasal insulin rapidly increases insulin levels in cerebrospinal fluid (CSF) without any measurable changes in peripheral insulin levels, suggesting insulin remains in the CNS. Multiple studies have shown that intranasal insulin can benefit a variety of measures including weight management, food intake, mood and cognition (Chapman et al., 2013). Pro-cognitive effects have been observed in both healthy and disease states, including T2DM, AD, mild cognitive impairment (MCI) and mood disorders (McIntyre et al., 2012; Benedict et al., 2011; Benedict et al., 2007a; Benedict et al., 2007b; Reger et al., 2006). One RCT on bipolar depression showed

Table 1
Summary of therapeutic treatments.

	Target	Treatment response
Intranasal Insulin	Increase brain insulin signalling	Non-invasive, pro-cognitive effects such as memory enhancement have been observed in both healthy and disease states, including T2DM, AD, mild cognitive impairment (MCI) and mood disorders. (McIntyre et al., 2012; Benedict et al., 2011; Benedict et al., 2007a; Benedict et al., 2007b; Reger et al., 2006) Sex and ApoE genotype may be covariates in response.
Intranasal IGF-I	Increase brain insulin signalling/ associated pathways	Pre-clinical models have shown positive anti-depressant effects.(Paslakis et al., 2012) IGF-I has a similar affinity for the IR, suggesting that the therapeutic effects of intranasal IGF-I may be mediated by both IGF-I receptors and IR. Clinical studies are needed.
Intranasal IGF-II	Activate pathways associated with brain insulin signalling	Vascular injections of IGF-II into rodent models have significantly enhanced memory retention and consolidation, however, systemic administration in humans has shown to induce hypoglycemia.(Chen et al., 2011; Clemmons et al., 2005)
PPAR-γ Agonists	Improve insulin sensitivity	Pre-clinical models have shown improvements in insulin-sensitive synaptic plasticity, as well as reductions in visceral fat and inflammation, and increased insulin sensitivity.(Combs et al., 2000; Kintscher and Law, 2005; Kemp et al., 2012) Clinical evaluation of PPAR-γ agonist in adults with MDD showed reduced depressive symptoms associated with improvements in glucose metabolism. (Kemp et al., 2012) Improvements in attention and memory have also been observed in AD.(Watson et al., 2005)
Glucagon-Like Peptide I Activation	Improve insulin sensitivity	Dipeptidyl peptidase 4 (DPP-4) inhibitors which prolong GLP-I have shown to improve cognitive function and restore brain insulin homeostasis in pre-clinical models.(Sa-Nguanmoo et al., 2017; Pintana et al., 2016; Pipatpiboon et al., 2013; Pintana et al., 2013) Mansur and colleagues demonstrated an association with a GLP-I receptor agonist and improved executive functioning as well as increased gray matter volume in brain regions subserving cognition for individuals with depression.(Mansur et al., 2017a; Mansur et al., 2017b)
CBT	Reduce depressive symptoms	CBT has shown significant reductions in depressive symptoms in addition to improvements in insulin sensitivity.(Shomaker et al., 2017)
Exercise	Improve insulin sensitivity and reduce depressive symptoms	Several clinical studies have shown exercise improves neurocognition, enhances insulin sensitivity, mitigates depressive symptoms and reduces the likelihood of depression.(Yaribeygi et al., 2019; Sampath Kumar et al., 2018)

administration of intranasal insulin for 8 weeks could improve executive functioning in adults, however this has not been observed in MDD (McIntyre et al., 2012; Cha et al., 2017). Sex and ApoE genotype may need to be considered when evaluating cognitive response to intranasal insulin as this has been a significant covariate for intranasal insulin use in adults with MCI or AD (Claxton et al., 2013).

Intranasal insulin has shown to improve multiple aspects of memory including immediate memory, delayed recall memory, and verbal memory, all of which are forms of hippocampus-dependent declarative memory (Benedict et al., 2011). One potential mechanism by which insulin induces these pro-cognitive effects is by modifying functional connectivity in brain regions responsible for memory and cognition. Zhang and colleagues demonstrated intranasal insulin can increase bilateral connectivity between hippocampi for patients with T2DM (Zhang et al., 2015). Intranasal insulin has also shown to acutely improve visuospatial memory and verbal fluency for individuals with T2DM (Novak et al., 2014). Improvement in attention-related tasks was postulated to be associated with insulin-induced vasodilation in the insular cortex (Kivimaki et al., 2009). Only a few studies have evaluated intranasal insulin for individuals with mood disorders which have mixed results, but evidence from insulin resistant T2DM and AD studies suggest intranasal insulin should still be explored as a target of interest in large controlled clinical trials for individuals with depression (McIntyre et al., 2012; Cha et al., 2017).

Intranasal IGF has also been postulated as a potential therapeutic target as pre-clinical models have shown positive anti-depressant effects (Paslakis et al., 2012). IGF-I has a synergistic effect with hippocampal BDNF and may be involved in the biological mechanism for conventional antidepressants improving symptoms of depression. Blocking IGF-I receptors abolishes the increase in hippocampal BDNF after antidepressant administration, suggesting administering IGF-1 may have anti-depressant or pro-cognitive effects in the hippocampus (Kazanis et al., 2004). Given that BDNF functioning is altered in depression, IGF-I may improve neurotrophic processes in the brain (Phillips, 2017). Moreover, IGF-I levels also increase in the CSF following conventional antidepressant treatment or physical exercise, in which both are associated with an improvement in mood and cognition (Paslakis et al., 2012). IGF-I has a similar affinity for the IR, suggesting that the therapeutic effects of intranasal IGF-I may be mediated by both IGF-I receptors and IR.

Vascular injections of IGF-II into rodent models have significantly enhanced memory retention and consolidation, however, systemic administration in humans has shown to induce hypoglycemia. (Chen et al., 2011; Clemmons et al., 2005). IGF-II has a much lower affinity for IR and therefore will likely only have a therapeutic effect through IGF-II receptors. Intranasal administration of IGF-II should be explored as a potential novel intervention target for treating cognitive dysfunction in depression.

4.1.1. PPAR-γ agonists

PPAR-γ agonists are insulin sensitizers commonly prescribed for the treatment of hyperglycemia in T2DM and metabolic syndrome; examples of include pioglitazone and rosiglitazone (Blázquez et al., 2014; Wang et al., 2014). Notably, pioglitazone has been shown to decrease visceral fat, reduce inflammation and increase insulin sensitivity (Combs et al., 2000; Kintscher and Law, 2005). PPAR-γ agonists are also able to effectively cross the BBB making it a compelling target for brain insulin resistance (Abdul-Ghani et al., 2015). Animal models of insulin resistance (i.e., rodents fed a high fat diet [HFD]) have shown that rosiglitazone can not only reverse the effects of peripheral insulin resistance, but also improve insulin-induced synaptic plasticity for learning and memory, as well as enhance neuronal Akt/PKB- ser phosphorylation in response to insulin (Kemp et al., 2012). In addition, the PPAR-γ agonists have shown to reverse mitochondrial dysfunction that was induced by the HFD in animal models by preventing mitochondrial swelling, decreasing ROS production, and reducing brain mitochondrial membrane potential changes during mitochondrial oxidative stress (Pipatpiboon et al., 2012). In a 12-week open label clinical study by Kemp and colleagues, administration of pioglitazone in adults with MDD showed that improvements in depressive symptoms were associated with improvements in glucose metabolism in insulin-resistant patients (Kemp et al., 2012). Cognitive impairment also has improved in individuals with AD, specifically in subsets of attention and memory; however, rosiglitazone also affected cardiovascular outcomes (Watson et al., 2005). In sum, PPAR-γ agonists, specifically pioglitazone, have great promise in improving cognitive dysfunction associated

with brain insulin resistance and future trials are warranted.

4.2. Glucagon-like peptide I activation

Glucagon-like peptide I (GLP-I) is a gut derived incretin that is beneficial in glycemic control and helps improve insulin sensitivity while reducing appetite and food intake (Drucker and Nauck, 2006; Gault et al., 2013). GLP-I has also shown to modulate synaptic transmission in brain regions subserving reward and cognition, as well as regulate neuronal excitability, survival and proliferation (McIntyre et al., 2013; Liu and Pang, 2016). DPP-4 inhibitors, such as vildagliptin, are oral antidiabetic drugs that inhibit DPP-4 activity and prolong the activation of GLP-I (Sa-Nguanmoo et al., 2017). Preclinical studies postulate that DPP-4 inhibitors can counteract the effects of brain insulin resistance and reduce cognitive impairment. HFD insulin-resistant animal models which present systemic inflammation, mitochondrial dysfunction, impaired hippocampal plasticity, brain apoptosis and cognitive dysfunction were used to evaluate DPP-4 inhibitors (Pintana et al., 2016; Pintana et al., 2015). Cognitive function improved alongside restored brain insulin resistance, improved mitochondrial function and reduced oxidative stress, as evidenced by a reduction in malondialdehyde (an end-product of lipid peroxidation), in several studies (Sa-Nguanmoo et al., 2017; Pintana et al., 2016; Pipatpiboon et al., 2013; Pintana et al., 2013). However, one study with testosterone derived rodents only had improved brain insulin resistance with no improvement in cognition, suggesting there may be a sex hormone interaction effect (Pintana et al., 2015). Other studies have also suggested brain insulin resistance may be sex-specific because of gonadal hormone interactions (Pratchayasakul et al., 2011). This highlights the complexity and multilevel interaction of insulin signalling.

Clinical trials have shown promising results with the therapeutic intervention of DPP-4 inhibitors, as well as other GLP-I pathway activators like liraglutide, a GLP-I receptor agonist. Mansur and colleagues demonstrated that liraglutide is associated with an improvement in executive functioning as well as increased gray matter volume in brain regions subserving cognition for individuals with depression (Mansur et al., 2017a; Mansur et al., 2017b). Although DPP-4 inhibitors have not shown to reduce depressive symptoms, future larger trials should continue to evaluate both anhedonia and pro-cognitive effects (Gamble et al., 2018).

4.3. Cognitive behavioural therapy

Notably, repurposing therapies which are primarily used to treat depressive symptoms have also been shown to improve insulin sensitivity. For example, in a parallel randomized control trial by Shomaker and colleagues, researchers measured the long-term effects of a CBT intervention relative to a health education program on insulin sensitivity for adolescents with clinically-significant depressive symptoms who were at-risk for T2DM. The results revealed that both programs were associated with significant reductions in depressive symptoms in addition to improvements in insulin sensitivity (Shomaker et al., 2017). Therefore, impairments in insulin signalling may be both a preclinical risk factor as well as a result of depression, suggesting there is a common biological substrate that can be targeted in treatment.

4.4. Exercise

Exercise has profound beneficial effects on the brain. The neurocognitive enhancing effects of exercise have been well documented across multiple brain disorders and are thought to mediate their effects via disparate neurobiological systems including, but not limited to neurogenesis, neurotrophism, immunoinflammation and insulin sensitivity mechanistic pathways (Solé et al., 2017). Exercise is thought to improve insulin sensitivity by reducing pathological processes such as production of adipokines, inflammation and oxidative stress (Yaribeygi et al., 2019; Sampath Kumar et al., 2018). Moreover, regular exercise has been demonstrated in the general population (regardless of intensity) to reduce the incidence of MDD (Harvey et al., 2018). It is also established that exercise mitigates depressive symptoms to a greater extent when compared to a controlled intervention (Kvam et al., 2016). Therefore exercise may be implemented as both a preventative measure for depression and as a therapeutic agent (Carek et al., 2011).

5. Conclusion & future directions

Depression is both a cognitive and metabolic disorder. There is a bidirectional relationship between brain insulin resistance and depression evidenced by their high rate of comorbidity, which suggests there is a common biological substrate. A metabolic disease model of depression should be considered as conventional treatment is symptom suppressive and not disease modifying. Insulin has powerful neuromodulatory, neuroprotective and neurotrophic effects on the brain and brain insulin resistance may be responsible for the cognitive and anhedonia-like symptoms in depression. Hitherto, there is no consensus on the definition of brain insulin resistance and it is imperative one be established to improve the efficacy and congruency amongst research studies. Based on the collection of pre-clinical and clinical data, repurposing insulin-sensitizing agents for the treatment of depressive symptoms may be an effective pathoetiological targeting therapy. Clinical trial evidence is essential in exploring these novel insulin-targeting therapeutic interventions. Screening for insulin resistance in patients with depression at onset is warranted to characterize treatment response.

Disclosures

None.

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