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Review article

Insulin resistance and hippocampal dysfunction: Disentangling peripheral and brain causes from consequences

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ABSTRACT

In the periphery insulin plays a critical role in the regulation of metabolic homeostasis by stimulating glucose uptake into peripheral organs. In the central nervous system (CNS), insulin plays a critical role in the formation of neural circuits and synaptic connections from the earliest stages of development and facilitates and promotes neuroplasticity in the adult brain. Beyond these physiological roles of insulin, a shared feature between the periphery and CNS is that decreases in insulin receptor activity and signaling (i.e. insulin resistance) contributes to the pathological consequences of type 2 diabetes (T2DM) and obesity. Indeed, clinical and preclinical studies illustrate that CNS insulin resistance elicits neuroplasticity deficits that lead to decreases in cognitive function and increased risk of neuropsychiatric disorders. The goals of this review are to provide an overview of the literature that have identified the neuroplasticity deficits observed in T2DM and obesity, as well as to discuss the potential causes and consequences of insulin resistance in the CNS, with a particular focus on how insulin resistance impacts hippocampal neuroplasticity. Interestingly, studies that have examined the effects of hippocampal-specific insulin resistance illustrate that brain insulin resistance may impair neuroplasticity independent of peripheral insulin resistance, thereby supporting the concept that restoration of brain insulin activity is an attractive therapeutic strategy to ameliorate or reverse cognitive decline observed in patients with CNS insulin resistance such as T2DM and Alzheimer's Disease.

1. Introduction

Insulin is synthesized and secreted by pancreatic β cells and once released into systemic circulation binds to insulin receptors to stimulate glucose uptake in peripheral tissues like muscle, heart and fat. In metabolic disorders such as type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome, this delicate homeostatic mechanism through which insulin regulates glycaemia is disrupted as a result of decreases in insulin receptor expression and/or activity (i.e. insulin-resistance). Given its important role in glucose homeostasis, it is unsurprising that early studies that examined insulin activity under physiological or pathological conditions focused almost exclusively on the peripheral actions of insulin. This peripherally-focused view of insulin signaling was challenged in the 1960s when seminal findings determined that insulin acting directly in the central nervous system (CNS) regulated blood and cerebrospinal fluid glucose levels, as well as cerebral metabolism [for review see (Rafaelsen, 1967)]. Subsequent studies identified widespread localization of insulin receptor binding activity in the rodent brain in regions such as the hypothalamus, cortex and hippocampus (Havrankova et al., 1978). While the identification of insulin binding sites in the hypothalamus were not unexpected given the ability of central insulin to regulate glucose homeostasis, localization of insulin receptors in brain regions such as the cortex and hippocampus suggested that insulin may be involved in other activities beyond glucose homeostasis, such as cognitive function. Such observations initiated a heightened awareness that the activities of insulin extended to the CNS and began to dispel the long-standing notion that the brain was an 'insulin-insensitive' organ.

Our understanding of CNS insulin activity continues to evolve, especially in the context of how insulin resistance is a mechanistic mediator of the neurological complications of many metabolic disorders, neuropsychiatric disorders and age-related cognitive decline. However, determination of the relative contribution of insulin resistance in neuroplasticity deficits is complicated by the fact that

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metabolic disorders are characterized by a variety of endocrine abnormalities, including glucose intolerance, leptin resistance and dyslipidemias, as well as increases in pro-inflammatory mediators and oxidative stress. Moreover, insulin resistance is not generalizable to metabolic disorders in that insulin resistance is not universally observed in obese patients and rodents. As such, clinical and preclinical studies cannot definitively and/or exclusively attribute insulin resistance as the cause of neuroplasticity deficits observed in metabolic disorders or aging (Reagan, 2012). However, as will be described below, molecular approaches that more selectively target brain insulin receptor expression and activity are beginning to tease apart the role of insulin resistance from the other endocrine changes observed in many metabolic disorders. Accordingly, our review will contrast the relative contributions of peripheral metabolic and endocrine deficits with brain region-specific insulin resistance in the development of hippocampal neuroplasticity deficits in obesity and T2DM.

2. Neuroplasticity deficits in metabolic disorders

Clinical and epidemiological data clearly indicate that patients with metabolic disorders exhibit structural and functional deficits in the CNS that include cognitive dysfunction and increased risk of developing neuropsychiatric disorders like depressive illness (Chatterjee et al., 2016; Pedditizi et al., 2016; Biessels et al., 2014; Anderson et al., 2001; Ali et al., 2006). Experimental models of obesity and T2DM support these clinical observations (Cordner and Tamashiro, 2015). For example, pioneering studies by Greenwood and Winocur demonstrated that rats provided a high fat diet (HFD) exhibited deficits in hippocampal-dependent learning and memory (Greenwood and Winocur, 1990). Subsequent studies confirmed these initial observations in HFD rodents [see (Boitard et al., 2012; Stranahan et al., 2008b; Kanoski et al., 2010; Greenwood and Winocur, 1996) as examples], as well as in other models of obesity/T2DM such as *db/db* mice and Zucker rats [see (Stranahan et al., 2008b; Li et al., 2002) as examples]. While not discounting the potential contributions of other peripheral endocrine changes, hippocampal insulin resistance has been identified as a mechanistic mediator of these behavioral deficits in HFD rats (McNay et al., 2010) and Zucker rats (Winocur et al., 2005).

In addition to deficits in hippocampal-dependent behavioral learning and memory tasks, obese and diabetic rodents also exhibit increases in depressive-like behaviors. For example, *ob/ob mice* (Collin et al., 2000; Yamada et al., 2011), *db/db* mice (Sharma et al., 2010) and mice provided a HFD (Yamada et al., 2011) exhibit increased immobility behavior in the forced swim test, which is considered to be indicative of behavioral despair. HFD mice also exhibit anhedonia in the sucrose preference test (Yamada et al., 2011). In order to avoid potential developmental confounds of genetic models of metabolic syndromes and the cumulative effects of central and peripheral endocrine changes in HFD models, we recently examined the metabolic and neurobehavioral effects elicited by a peripherally-acting leptin receptor antagonist in adult rats (Macht et al., 2017). Similar to observations in genetic models and HFD models, leptin receptor antagonism elicited increases in food intake, body weight and body fat, and also increased peripheral inflammation and insulin resistance. Leptin receptor antagonist-treated rats also exhibited behavioral despair in the forced swim test (Macht et al., 2017; Van Doorn et al., 2017). Collectively, these preclinical studies illustrate that metabolic disorders are associated with neurocognitive deficits that include impairments in learning and memory tests and development of depressive-like behaviors.

Beyond behavioral deficits, pre-clinical studies have also identified functional and structural deficits in hippocampal neuroplasticity in experimental models of T2DM and obesity. For example, impairments in stimulus-evoked long term potentiation (LTP), which is proposed to be a cellular correlate of learning and memory, is impaired in the hippocampus of obese Zucker rats (Gerges et al., 2003; Alzoubi et al., 2005), in *db/db* mice (Li et al., 2002) and in rodents provided a HFD (Stranahan et al., 2008b; Karimi et al., 2013). Morphological deficits have also been observed in experimental models of T2DM and obesity that include decreases in spine density, as well as decreased expression of synaptic proteins critical for neuronal functional activity (Stranahan et al., 2009; Arnold et al., 2014). Neurogenesis is also reduced in the dentate gyrus of HFD rats (Lindqvist et al., 2006), HFD mice (Hwang et al., 2008) and *db/db* mice (Stranahan et al., 2008a). In view of the critical role of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) in facilitating structural and functional plasticity in the CNS (Monteggia et al., 2004), it is not surprising that BDNF expression is also reduced in the hippocampus of obese rodents (Grillo et al., 2011c; Molteni et al., 2002; Stranahan et al., 2009). Collectively, these studies demonstrate that many measures of hippocampal synaptic plasticity are reduced in rodent models of T2DM and obesity. As noted above, metabolic disorders consist of a complex endocrine and metabolic milieu and as such a number of different factors likely contribute to these neurological complications in T2DM and obesity. Among the potential causes of these neuroplasticity deficits is brain insulin resistance.

3. Selective induction of brain insulin resistance: hypothalamic studies

While the studies above indicate that neuroplasticity deficits are observed in experimental models of T2DM and obesity, identification of the relative contribution of peripheral and/or CNS insulin resistance would require more selective targeting of different insulin receptor populations. In support of this experimental approach, seminal observations by Woods and co-workers demonstrated that chronic intracerebroventricular administration of insulin decreases food intake and body weight, suggesting that activation of brain insulin receptors plays a critical role in metabolic and endocrine homeostasis (Woods et al., 1979). Subsequent studies confirmed and extended these initial observations through the use of approaches to reduce brain insulin receptor activity or by more selectively targeting hypothalamic insulin receptor populations. For example, global knockout of brain insulin receptors induces a wide variety of metabolic disturbances in mice that included increases in food intake, body weight and adiposity, as well as endocrine disturbances such as increases in plasma levels of leptin and triglycerides (Bruning et al., 2000). More selective targeting of hypothalamic insulin receptor populations produced similar findings. For example, antisense oligonucleotide-mediated downregulation of hypothalamic insulin receptors elicited metabolic and endocrine changes that included increases in food intake and increases in subcutaneous fat depots (Obici et al., 2002a; Obici et al., 2002b). Interestingly, these studies also determined that downregulation of hypothalamic insulin receptors induced hepatic insulin resistance, thereby identifying an important role for hypothalamic insulin receptors in peripheral glucose homeostasis. More recently we developed a lentiviral vector packaged with an antisense sequence specific for the insulin receptor (LV-IRAS) and used this viral vector to selectively target hypothalamic insulin receptors. Consistent with these other observations, we reported that lentivirus-mediated downregulation of insulin receptors expressed in the arcuate nucleus increased food intake, body weight and subcutaneous fat depots and induced endocrine changes that included increases in plasma levels of leptin and triglycerides (Grillo et al., 2007; Grillo et al., 2014). Interestingly, rats with this hypothalamic-specific insulin resistance cleared glucose as effectively as control rats in response to an oral glucose tolerance test (Grillo et al., 2007). This lack of glucose intolerance is consistent with some (Bruning et al., 2000) but not all (Obici et al., 2002a; Obici et al., 2002b) of the studies described above. However, more discrete targeting of hypothalamic insulin receptor populations provided insight into the potential mechanisms responsible for the different metabolic outcomes of these studies. In this regard, LV-IRAS-mediated downregulation of insulin receptors expressed in the ventromedial hypothalamus (VMH) induced glucose

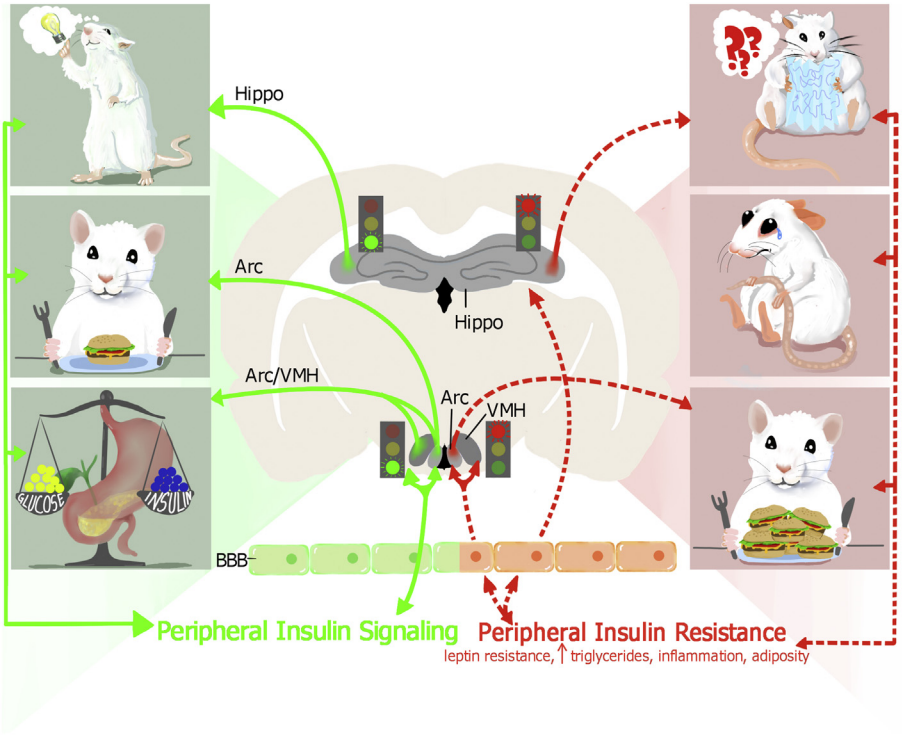

Fig. 1. Dissociation of functional activities of hypothalamic and hippocampal insulin receptor populations. While the hypothalamus has long been recognized as a key integration center for the regulation of food intake, body weight, body composition and metabolic functions, more recent studies have determined that these activities are compartmentalized within the hypothalamus. For example insulin receptors in the arcuate nucleus (Arc) are proposed to regulate feeding behavior while insulin receptor populations in the Arc and ventromedial hypothalamus (VMH) regulate glucose homeostasis and hepatic insulin sensitivity (green arrows). Additional studies have demonstrated that activation of hippocampal insulin receptors enhances cognition. However, hypothalamic-specific insulin resistance elicits peripheral metabolic changes that include insulin resistance, glucose dysregulation, leptin resistance and increases in inflammation (red dashed lines). These peripheral changes further exacerbate CNS insulin resistance, which likely contribute to the development of hyperphagia. These peripheral endocrine changes in combination with brain insulin resistance also impair hippocampal neuroplasticity, which likely contributes to the increased risk of neuropsychiatric disorders such as depressive illness and neurocognitive dysfunction. See text for details. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

intolerance and hepatic insulin resistance but did not modulate food intake (Paranjape et al., 2011). Such results indicate that while insulin receptors expressed in the arcuate nucleus may play a more important role in the modulation of body weight, body composition and food intake, insulin receptors expressed in both the arcuate nucleus and the VMH regulate glucose homeostasis and hepatic insulin sensitivity. Collectively, these data support the concept that the hypothalamus is a critical brain region in the regulation of body weight and metabolism and suggest that the functional activities of insulin receptors may be discretely compartmentalized within the hypothalamus; see Fig. 1.

In view of the hippocampal neuroplasticity deficits observed in experimental models of T2DM and obesity described above, we were interested in determining whether metabolic stress initiated by lentivirus-mediated induction of hypothalamic-specific insulin resistance would adversely affect hippocampal synaptic plasticity. These studies determined that rats with hypothalamic-specific insulin resistance exhibited a wide range of hippocampal neuroplasticity deficits when compared to control rats, including reductions in high frequency stimulation-mediated induction of LTP in the CA1 region of the hippocampus, as well as reduced Ser845 phosphorylation of hippocampal GluA1 receptor subunits (Grillo et al., 2011a). Since phosphorylation is a critical step for synaptic trafficking of AMPA receptor subunits (Oh et al., 2006), reductions in Ser845 pGluA1 may contribute to the deficits in LTP observed in the hippocampus of rats with hypothalamic-specific insulin resistance. Reductions in hippocampal expression of BDNF in rats with targeted downregulation of hypothalamic insulin receptors may also contribute to deficits in stimulus-evoked LTP in the CA1 region (Grillo et al., 2011c). This hypothesis is based on prior studies demonstrating that BDNF knockout mice exhibit deficits in hippocampal LTP (Korte et al., 1995; Patterson et al., 1996) and that these electrophysiological deficits can be reversed by bath application of BDNF (Patterson et al., 1996). Rats with hypothalamic-specific insulin resistance also exhibit morphological changes that include clustering and redistribution of presynaptic and postsynaptic proteins in the CA3 and CA1 regions of the hippocampus (Grillo et al., 2011b). Ultimately, these neuroplasticity deficits are likely responsible for the deficits in hippocampal-dependent behaviors (Grillo et al., 2011b) and the development of depressive-like behaviors (Grillo et al., 2011c; Grillo et al., 2014) observed in rats with hypothalamic-specific insulin resistance. These results illustrate that insulin resistance initiated in the hypothalamus elicits the development of a metabolic syndrome phenotype and impairs hippocampal synaptic plasticity. Moreover, these results support the concept that insulin resistance in both the periphery and the CNS contributes to the development of neuroplasticity deficits in T2DM and obesity. Unfortunately, one limitation to these studies is that they cannot selectively examine the role of hippocampal insulin receptors in brain dysfunction associated with metabolic disorders.

4. Insulin and cognitive function: focus on the hippocampus

Whereas insulin receptors expressed in the hypothalamus regulate feeding, body weight and metabolism, hippocampal insulin receptors are proposed to regulate cognitive function. For example, intracerebroventricular insulin administration to healthy adult rodents enhances behavioral performance in the passive avoidance test (Park et al., 2000), while intrahippocampal insulin administration enhances performance in alternation maze testing (McNay et al., 2010) and in the water maze (Moosavi et al., 2006). Clinical studies further support the concept that increasing brain insulin levels enhances cognitive function. In this regard, studies by Benedict, Hallschmid and coworkers have reported that chronic intranasal insulin administration enhances cognitive performance and mood in healthy adults (Benedict et al., 2004). Acute intranasal insulin administration has also been shown to enhance cognitive performance in healthy adult subjects (Novak et al., 2014). Mechanistically, the improvements in cognitive function and mood may result from increases in hippocampal functional connectivity (Zhang et al., 2015) and increases in vascular perfusion (Novak et al., 2014). At the synaptic level, insulin modulates the trafficking and phosphorylation state of glutamate receptor subunits, which may ultimately facilitate excitatory transmission of hippocampal neurons (De Felice and Benedict, 2015). Collectively, such observations support the concept that in the adult CNS insulin plays an important role in the development

and maintenance of a substrate upon which neuroplasticity can occur (Ferrario and Reagan, 2017).

5. Selective induction of brain insulin resistance: hippocampal studies

Interestingly, the mood and cognitive enhancing effects of intranasal insulin treatment were not associated with significant alterations in peripheral glucose homeostasis (Benedict et al., 2004; Hallschmid et al., 2008; Benedict and Grillo, 2018). The relative absence of metabolic changes following intranasal insulin administration further emphasizes that insulin receptors expressed in the hypothalamus and hippocampus mediate distinctly different functional activities. Nonetheless, deficits in cognition and hippocampal neuroplasticity are consistently observed in metabolic disorders that include insulin resistance. As a result, it can be challenging to disentangle the relative contributions of peripheral and CNS endocrine and metabolic changes to deficits in hippocampal neuroplasticity observed in T2DM and obesity.

A major question facing clinical and preclinical scientists is whether hippocampal insulin resistance contributes to the cognitive deficits and increased risk for neuropsychiatric disorders observed in patients with metabolic disorders (Biessels and Reagan, 2015). In order to address this question, we injected the LV-IRAS construct bilaterally into the rat hippocampus (Hippo-IRAS) in order to induce hippocampal-specific insulin resistance and then examined different aspects of hippocampal synaptic plasticity (Grillo et al., 2015). Hippo-IRAS rats did not exhibit any changes in body weight or body composition compared to rats that received bilateral hippocampal injections of the LV-Control construct (Hippo-Con). Additionally, Hippo-IRAS rats did not exhibit any changes in peripheral glucose homeostasis, insulin sensitivity or stress reactivity compared to Hippo-Con rats. Collectively, downregulation of hippocampal insulin receptors did not elicit peripheral metabolic or endocrine changes that are characteristic of metabolic disorders, thereby allowing for the more selective assessment of how hippocampal-specific insulin resistance impacts hippocampal synaptic plasticity. In this regard, rats with hippocampal-specific insulin resistance exhibited learning and memory impairments in the water maze, as well as deficits in stimulus-evoked LTP in the CA1 region and the dentate gyrus when compared to Hippo-Con rats. Paired-pulse facilitation was similar in both groups, suggesting a postsynaptic locus for the synaptic transmission deficits observed in Hippo-IRAS rats. In support of this concept, the expression and phosphorylation state of glutamate receptor subunits was reduced in the hippocampus of Hippo-IRAS rats. Collectively, these results illustrate that unlike physiological conditions in which insulin promotes and maintains synaptic plasticity, insulin resistance in the hippocampus directly impairs neuroplasticity.

6. Causes versus consequences of hippocampal insulin resistance

Beyond the assessment of how peripheral versus central insulin resistance impacts hippocampal synaptic plasticity, it is important to distinguish the causes and the consequences of hippocampal insulin resistance. Previous studies have identified increases in oxidative stress and pro-inflammatory cytokines, as well as impairments in the activity of the hypothalamic-pituitary adrenal (HPA) axis as causes of peripheral insulin resistance; i.e. these factors are ‘upstream’ of insulin resistance (Kwon and Pessin, 2013; Henriksen et al., 2011; Page et al., 1991). These results provide important starting points for the identification of mechanistic mediators of hippocampal insulin resistance in metabolic disorders (Fig. 2). For example, increases in oxidative stress is a well-characterized CNS complication of metabolic disorders that may impair insulin receptor activity (Gispen and Biessels, 2000). Moreover, we have previously shown that administration of stress levels of glucocorticoids induces both peripheral insulin resistance and hippocampal insulin resistance (Piroli et al., 2007). Additionally, elegant studies by Stranahan and coworkers have shown that excess glucocorticoids play a critical role in the neuroplasticity deficits observed in obese rodents (Stranahan et al., 2008a).

Neuroinflammation is also observed in rodents provided a high fat diet and may thereby be an important mediator of neuroplasticity deficits observed in rodent models of obesity (Pistell et al., 2010; Boitard et al., 2014; Gladding et al., 2018). While we previously reported that inflammation is increased in rats with hypothalamic-specific insulin resistance (Grillo et al., 2014), our ongoing studies determined that hippocampal levels of pro-inflammatory cytokines are not increased in rats with hippocampal-specific insulin resistance (Fig. 3). The absence of neuroinflammation in Hippo-IRAS rats suggests that similar to observations in the periphery, neuroinflammation is ‘upstream’ of insulin resistance in the hippocampus. More simply, neuroinflammation may be among the causative factors of CNS insulin resistance. Conversely, decreases in the expression of BDNF may be a consequence (i.e. downstream) of insulin resistance. Consistent with other studies using experimental models of T2DM and obesity (Kanoski et al., 2007; Stranahan et al., 2009; Molteni et al., 2002), rats with hypothalamic-specific insulin resistance exhibit decreases in plasma levels of BDNF (Grillo et al., 2011c; Grillo et al., 2014). Similarly, hippocampal-specific insulin resistance also decreases plasma levels of BDNF (Fig. 3). Such results indicate that decreased expression of BDNF is ‘downstream’ of insulin resistance (i.e. is a consequence of insulin resistance).

7. Therapeutic treatments that target brain insulin resistance

The preclinical studies described above clearly identify insulin resistance as a key mechanistic mediator of the neurological complications associated with metabolic disorders. As such, restoration of brain insulin activity may be an effective mechanism to ameliorate or reverse the neurocognitive dysfunction observed in T2DM patients. In support of this hypothesis, restoration of insulin sensitivity in the periphery and the CNS likely contributes to the pro-cognitive effects of physical activity in humans [for reviews see (Mattson, 2012; Hillman et al., 2008)]. Pre-clinical studies further support this hypothesis in that voluntary exercise (i.e. wheel running) can prevent (Molteni et al., 2004; Klein et al., 2016) and reverse (Noble et al., 2014) HFD-induced impairments in hippocampal synaptic plasticity. Other strategies that restore peripheral metabolic and endocrine measures, such as bariatric surgery (Grayson et al., 2014), mild food restriction paradigms (Grillo et al., 2011a; Grillo et al., 2014) and replacement of HFD with a control diet (Yamada et al., 2011), also reverse impairments in hippocampal synaptic plasticity. Collectively, such results further support the concept that peripheral changes are an important component of hippocampal dysfunction in insulin resistance states like T2DM and obesity.

An additional strategy to ‘indirectly’ restore brain insulin activity is through modulation of the incretins; glucagon-like peptide 1 (GLP) and glucose-dependent insulinotropic polypeptide (GIP). These gastrointestinal-tract derived peptides enhance glucose-dependent insulin release and administration of incretin analogues or inhibitors of dipeptidyl peptidase 4 (DPP4, which is responsible for the degradation of the incretins) are emerging strategies for the treatment of metabolic disorders. For example, preclinical studies have shown that incretin analogues and DPP4 inhibitors improve behavioral performance in HFD rodents (Pintana et al., 2013; Gault et al., 2010; Porter et al., 2010). Interestingly, these enhancements in behavioral performance may involve increases in hippocampal insulin receptor signaling (Pipatpiboon et al., 2013). These exciting preclinical data have been translated to the clinical setting in that ongoing studies are examining the efficacy of DPP4 inhibitors in the treatment of cognitive dysfunction in T2DM patients (Biessels et al., 2018). Similarly, targeting the incretin system may be a novel strategy in the treatment of age-related cognitive decline. A recent study by Rasgon and coworkers determined that administration of the incretin analogue liraglutide increases hippocampal

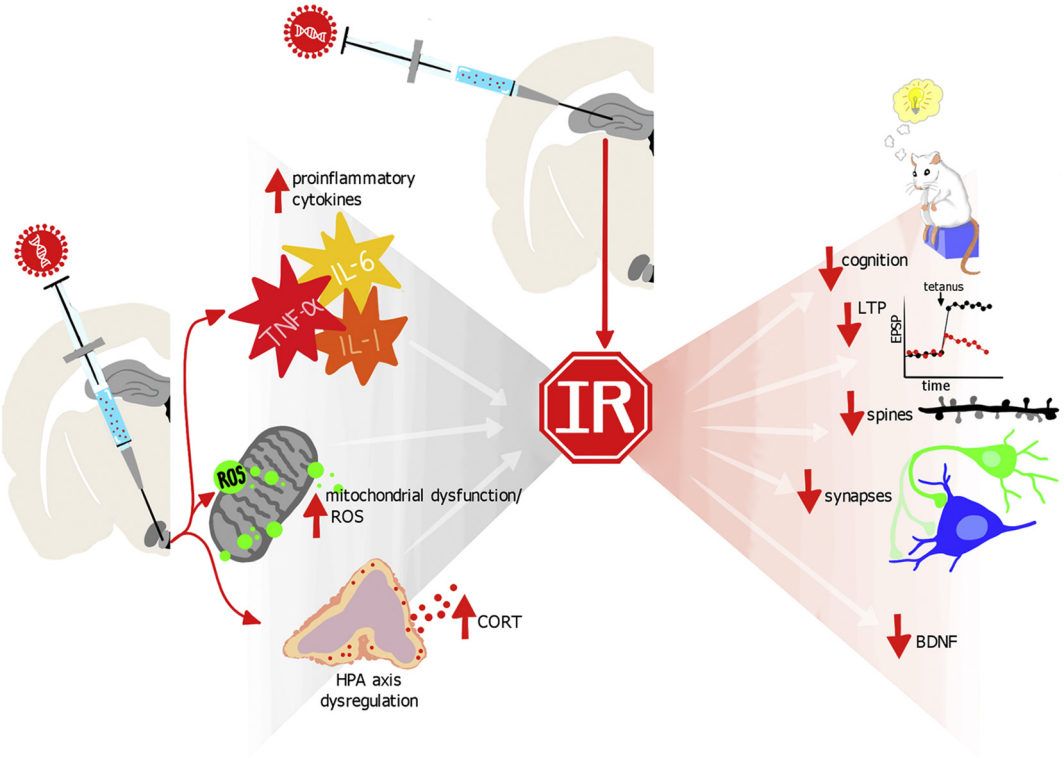

Fig. 2. Causes versus consequences of CNS insulin resistance. Similar to observations in the periphery, a number of factors have been identified as causes of CNS insulin resistance (IR in stop sign) in experimental models of obesity and diabetes. This includes increases in pro-inflammatory cytokines/neuroinflammation and increases in oxidative stress/reactive oxygen species (ROS) resulting from mitochondrial dysfunction, as well as dysregulation of the hypothalamic pituitary adrenal (HPA) axis that results in increases in CORT levels (cortisol in humans; corticosterone in rodents). These causes of insulin resistance are also induced by induction of hypothalamic-specific insulin resistance using an insulin receptor antisense construct, further emphasizing that neuroinflammation, mitochondrial dysfunction and HPA axis dysregulation, among other factors, are causes of hippocampal neuroplasticity deficits in metabolic disorders. Hippocampal-specific insulin resistance induced by insulin receptor antisense downregulation directly elicits neuroplasticity deficits independent of HPA axis dysregulation (Grillo et al., 2015) or neuroinflammation (See Fig. 3). Such results support the concept that in addition to the combined consequences of peripheral and CNS insulin resistance, CNS insulin resistance may act independently to elicit deficits in hippocampal synaptic plasticity. See text for details.

functional connectivity in subjects with increased risk of developing AD (Watson et al., 2019).

Approaches that directly target brain insulin activity have also yielded some provocative pro-cognitive results, most notably the ability of intranasal administration of insulin to enhance cognitive performance in obese humans without affecting glucose homeostasis or body composition (Hallschmid et al., 2008). Beyond metabolic disorders, post-mortem studies have demonstrated that hippocampal insulin resistance is correlated with cognitive decline in Alzheimer's Disease (AD) patients (Talbot et al., 2012). Such reports support prior studies demonstrating that insulin resistance is correlated with reductions in hippocampal formation volume and cognitive performance in individuals with increased risk of developing AD (Rasgon and Kenna, 2005; Rasgon et al., 2011). Based on these observations and others, enhancing brain insulin activity is recognized as an attractive strategy for the treatment of age-related cognitive decline (De Felice, 2013; Craft, 2007; Freiherr et al., 2013). Indeed, seminal observations by Craft and coworkers demonstrated that intranasal insulin administration improved cognitive performance in early stage AD patients (Craft et al., 2012; Reger et al., 2008). These exciting findings have been expanded in an ongoing clinical trial that is examining the structural and functional benefits of intranasal insulin administration in early stage AD patients (see ClinicalTrials.gov: NCT01767909). The important take home message from these studies is that promising lifestyle changes and pharmacological strategies are emerging that hold great promise for restoring brain insulin function and thereby enhancing neuroplasticity in patients with age-related cognitive decline and metabolic disorders such as obesity and T2DM.

8. Concluding remarks

While the studies described in this review have focused on insulin resistance, it is important to take the '30,000 foot view' and recognize that insulin resistance is among the components of the obesity/T2DM endocrine milieu that contributes to the development of hippocampal neuroplasticity deficits (Reagan, 2012). For example, as noted above leptin resistance is associated with impairments in hippocampal plasticity (Harvey et al., 2006), including impairments in cognitive function and development of neuropsychiatric disorders (Van Doorn et al., 2017). Interestingly, insulin receptors and leptin receptors activate similar signaling cascades, most notably the PI3-kinase/Akt pathway (Flak and Myers Jr, 2016; Biessels and Reagan, 2015). As such, leptin resistance and insulin resistance may act in an additive or synergistic fashion to impair hippocampal synaptic plasticity in metabolic disorders. Dyslipidemias in T2DM and obesity also likely contribute to vascular complications, which has been suggested as a mechanistic mediator of the neuroplasticity deficits associated with metabolic disorders (Brundel et al., 2014). When viewed from this broader context, the take home message is that a 30,000 ft treatment approach that includes a combination of the 'lifestyle' changes (i.e. weight loss; alterations in diet; exercise) and pharmacological approaches (incretin analogues/intranasal insulin) may be the most successful strategy for the effective management of cognitive decline in AD, T2DM and obesity.

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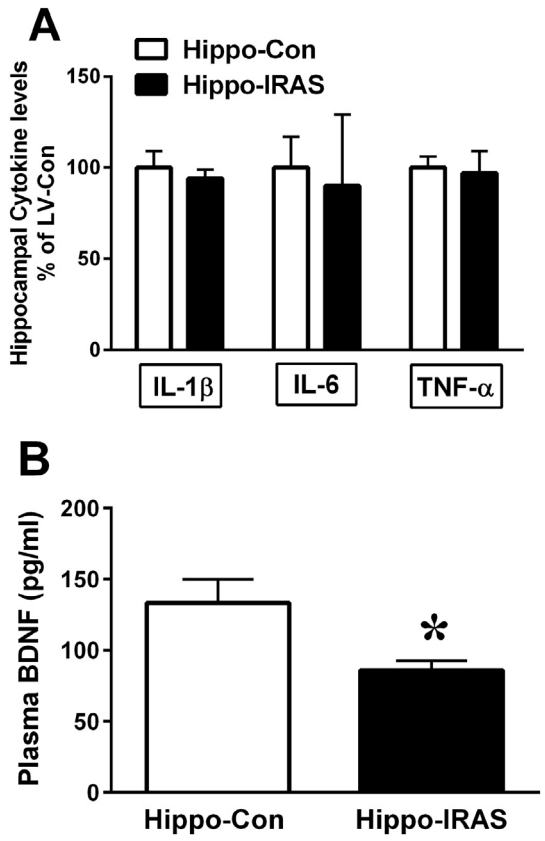

Fig. 3. Hippocampal-specific insulin resistance differentially impacts neuroinflammation and neurotrophic factor expression in the rat hippocampus. Panel A: To further investigate the potential causes and consequences of hippocampal insulin resistance, we examined hippocampal cytokine levels in rats with hippocampal-specific insulin resistance. Bio-Plex analysis was performed on hippocampal extracts from rats that received bilateral injections of a control lentivirus (Hippo-Con) or bilateral injections of an insulin receptor antisense-containing lentivirus (Hippo-IRAS). Hippocampal levels of pro-inflammatory cytokines were unchanged in Hippo-IRAS rats compared to Hippo-Con rats; IL-1β, IL-6 and TNF-α are provided as examples. Such results suggest that similar to observations in the periphery, neuroinflammation is 'upstream' of insulin resistance; i.e. neuroinflammation is a cause of CNS insulin resistance. Panel B: Hippocampal-specific insulin resistance decreases plasma levels of BDNF. We have previously shown that hippocampal-specific insulin resistance elicits deficits in hippocampal synaptic transmission and spatial learning and memory (Grillo et al., 2015). Given the proposed role of BDNF in hippocampal synaptic plasticity, we examined BDNF levels in plasma from the same cohorts of rats. ELISA analysis determined that plasma BDNF levels were significantly reduced in the rats with hippocampal-specific insulin resistance (Hippo-IRAS), suggesting that decreases in neurotrophic factor expression is a consequence (i.e. downstream) of hippocampal insulin resistance. [$t = 2.74$, $p < .01$].

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