Biochemical Pharmacology 84 (2012) 737–745

Contents lists available at SciVerse ScienceDirect

Biochemical Pharmacology

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

Commentary

Insulin resistance in the brain: An old-age or new-age problem?

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ARTICLE INFO

Article history:
Received 2 April 2012
Accepted 8 May 2012
Available online 16 May 2012

Keywords:
Diabetes
Dementia
Insulin resistance

ABSTRACT

Life expectancy is rising however with more people living longer there is a concomitant rise in the incidence of dementia. In addition to age-related cognitive decline there is a higher risk of going on to develop vascular dementia and Alzheimer's disease associated with aspects of modern lifestyle. Most worryingly, recent data reports accelerated cognitive decline in adolescents associated with poor diet (high fat and calorie intake). Thus the increase in dementia in 'old-age' may have as much to do with 'new-age' lifestyle as it does with normal ageing. It would seem wise therefore to investigate the molecular connections between lifestyle and cognitive decline in more detail. Epidemiological evidence suggests an increased risk of developing dementia (including Alzheimer's disease) in individuals with obesity and type 2 diabetes but also in those with poor insulin sensitivity without diabetes, implicating a mechanistic link between adiposity, insulin sensitivity and dementia. Insulin receptors are expressed in the brain and physiological roles for insulin in the CNS are starting to be delineated. Indeed disrupted neuronal insulin action may underlie the link between diabetes and neurodegenerative disorders. This review discusses the difficulties in quantifying insulin sensitivity of the brain and why it is vital that we develop technology for this purpose so that we can establish its role in this 'new-age' dementia. This has particular relevance to the design and interpretation of clinical trials in progress to assess potential benefits of insulin and insulin sensitisers on prevention of cognitive decline.

1. Diabetes and dementia

It has long been known that diabetes alters vascular function, hence it is perhaps not surprising that there is an increased risk of vascular dementia associated with diabetes [1]. However there is accumulating evidence that this is not the only effect of diabetes on the brain. Longitudinal studies have identified a higher risk of dementia or significant cognitive decline associated with type 2 diabetes mellitus (T2DM) and also insulin resistance without T2DM (for review see [2]). The increased risk means that in the 70- to 90-year old age group around 26% of people with dementia also have diabetes, and this compares to around 21% of the general population in this age group. Prospective studies confirm this association albeit with a lower magnitude of increased risk than retrospective analysis [3]. In both cases the increased risk is independent of vascular risk factors. Diabetes increases risk in three areas of cognitive function: the risk for older adults of cognitive decline; the rate of cognitive decline; and the risk of future dementia [3]. Alzheimer's disease (AD) is the most common cause of dementia among people with T2DM, while diabetes and impaired fasting glucose have been linked to increased risk of Mild Cognitive Impairment (MCI; [4]), which is also a significant dementia risk factor. Conditions associated with T2DM, in particular hypertension and obesity, are specifically linked to poor cognitive performance in men [5], and obesity in middle age is a risk factor for developing dementia in later life [6]. More recently the Hisayama Study found that impaired glucose tolerance (an early warning sign of T2DM) increased risk of all-cause dementia [7]. Duration of diabetes is also a risk factor for increased cognitive decline, and this may be related to length of exposure to high levels of insulin combined with severity of disease [8].

Taking all of these studies into consideration it seems unlikely that there will be a single major underlying cause for the increased risk of dementia associated with T2DM, however dysregulated glucose and insulin homeostasis is common to all populations studied. This raises the possibility that insulin resistance, or hyperinsulinaemia and impaired glucose tolerance associated with insulin resistance, enhances the progression of neurodegeneration, or synaptic loss, responsible for the symptoms of cognitive decline and dementia. This may include processes that promote amyloid or tangle pathology in AD. It will be important to establish whether the cognitive deficits and risk of AD associated with diabetes are also found associated with lean diabetes, where insulin resistance is not induced by high fat intake. In order to understand more about such processes it is necessary to first understand the physiological roles of insulin in the periphery and the CNS (which

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http://dx.doi.org/10.1016/j.bcp.2012.05.007

may not be identical of course), and also to define what is meant by the term 'insulin resistance'.

2. Molecular pathology of insulin resistance and diabetes

Diabetes is a disease defined by hyperglycaemia (≥7 mM fasting plasma glucose on two separate measures is the major diagnostic criteria of diabetes), with numerous related health problems including retinopathy, neuropathy, nephropathy, heart disease and stroke. Loss of beta cell function and hence insulin secretion is the most common cause of type 1 diabetes mellitus, while a reduced response to insulin in target tissues (generally referred to as insulin resistance) is a risk factor for as well as an early and common feature of T2DM. The most common T2DM therapeutic is metformin, which may elicit at least some of its benefits through improving insulin sensitivity.

Insulin resistance is a widely used but rather imprecise term. It refers to the fact that tissues do not respond sufficiently to physiological insulin concentrations, hence higher than normal insulin concentrations are required to maintain glucose homeostasis. Therefore newly diagnosed T2DM is usually associated with hyperinsulinaemia. It is well documented that poor insulin sensitivity is closely correlated with obesity and hyperlipidaemia. Meanwhile, animal models of obesity (e.g. the db/db and ob/ob mouse, or diet induced obese animals) have progressively declining insulin sensitivity prior to the development of T2DM [9,10]. This argues that obesity has a major influence on the development of insulin resistance, and is considered the underlying cause of the current epidemic of T2DM.

No clear diagnostic criteria exist to define insulin resistance, and in a healthy population there is huge variability in insulin sensitivity [11]. The most common technique for assessing whole body insulin sensitivity in cases where pancreatic beta cell function is maintained is the Homeostasis Model Assessment (HOMA). This index is based on fasting plasma insulin and glucose concentrations. However the gold standard technique for accurate assessment of insulin sensitivity is the hyperinsulinaemic–euglycaemic clamp (HEC). This measures the specific ability of a given amount of insulin to regulate plasma glucose concentration but requires several hours of clinic time to obtain, making it only viable in specialised clinical research groups.

The molecular pathology of insulin resistance remains controversial. It could be related to development of a post-receptor defect reducing the insulin 'sensing' or 'signalling' capacity of individual cells [9]. This, in turn, results in a requirement for higher levels of insulin to stimulate glucose uptake into muscle, to reduce glucose production in liver and to correctly regulate adipose tissue. In addition, it is assumed that obesity occurs prior to a post-receptor defect, and indeed promotes the defect(s), although this has not been formally proven in man. Indeed, as insulin is proposed to regulate hypothalamic control of satiety (see later) it is interesting to speculate that insulin resistance in the hypothalamus may contribute to development of obesity. Consistent with this possibility animal studies have identified molecular lesions of the insulin signalling pathways that produce obesity. In addition, infusion of the adipokine leptin to the obese ob/ob mouse (which lacks leptin) has clear beneficial effects on glucose metabolism prior to reduction in body mass, while recent evidence from gastric bypass surgery suggests improvement in insulin sensitivity prior to weight loss. Therefore the relationship between obesity and insulin sensitivity may not be as unidirectional as currently proposed.

If the development of insulin resistance occurs as a consequence of defective post-receptor signalling then the earliest measure of insulin resistance should be a specific defect(s) in intracellular insulin signalling, and these should be detectable in tissue samples from insulin resistant individuals (Fig. 1). This has been attempted in only a few human studies where insulin sensitivity has also been quantified by HEC [12]. At this time it is not clear what molecular lesion in liver, muscle and fat of human patients is responsible for development of insulin resistance and ultimately T2DM, or if every tissue develops insulin resistance by the same route. One widely touted mechanism involves the downregulation of insulin receptor substrate (IRS) proteins (Fig. 2),

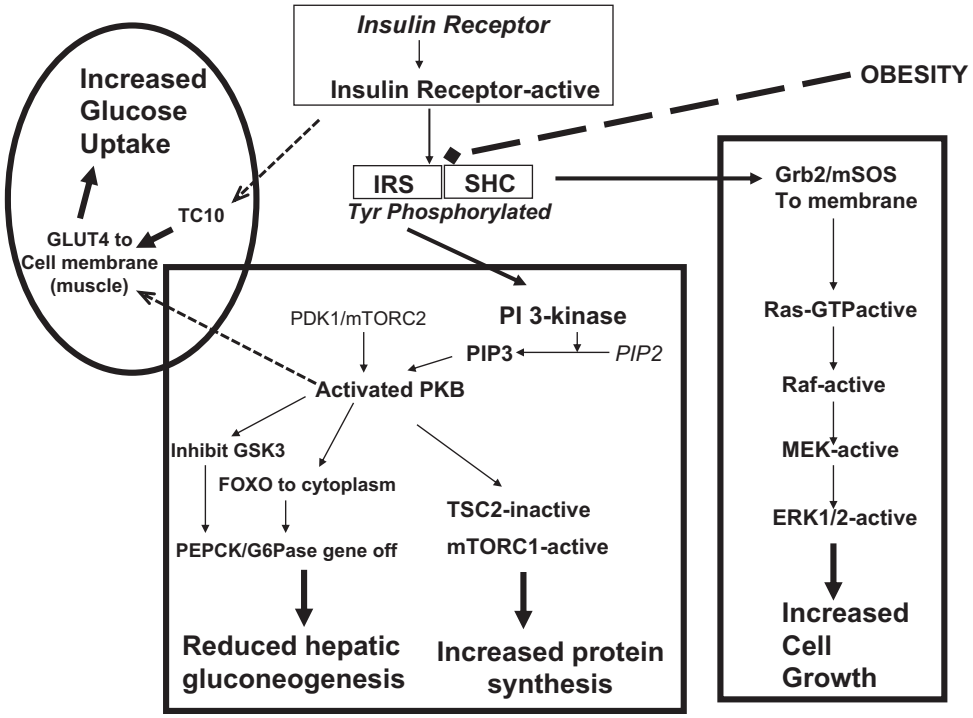

Fig. 1. Simplified diagram of insulin signalling pathways thought to regulate glucose uptake (muscle and adipose tissue), gluconeogenesis (liver), protein synthesis and cell growth (general).

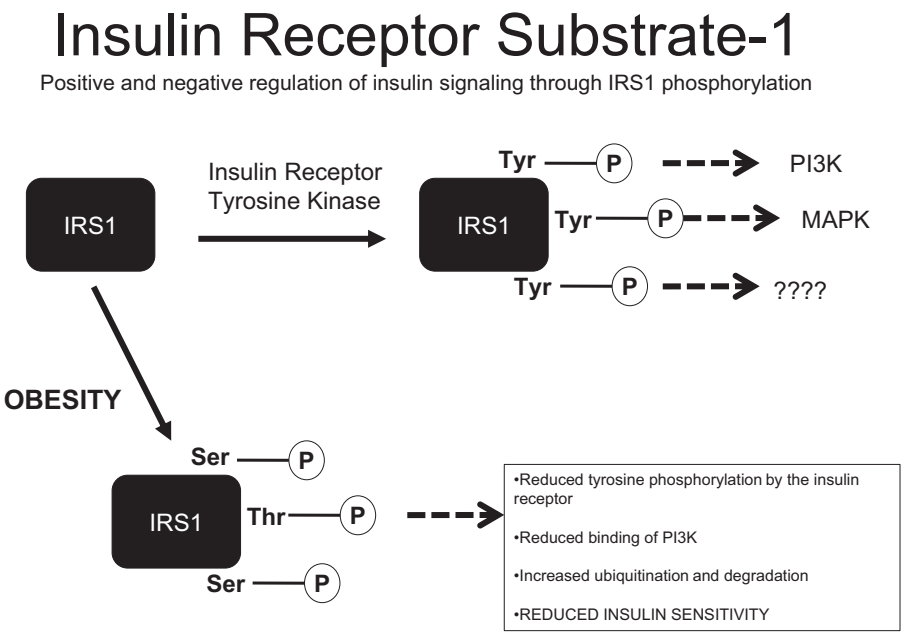

Fig. 2. Model of potential molecular site for obesity induced insulin resistance. Insulin signalling through IRS1 is abrogated by post-translational modification of IRS1 in response to obesity leading to its degradation.

in response to hyperlipidaemia and inflammation [13,14]. However it seems likely that there will not be one single molecular problem that promotes insulin resistance and T2DM, and this may partly explain why there is such variability in response to diabetes therapeutics. Therefore the analysis of intracellular signalling pathways in specific tissues may prove to be a means to establish the insulin sensitivity of each tissue. This is most important in the more unusual insulin target tissues such as the brain, where tissue insulin sensitivity currently cannot be assessed by HOMA or clamp techniques. Indeed there are no accurate techniques available at present even to establish that animal or cell models truly exhibit 'neuronal insulin resistance'.

3. Insulin action in the periphery

The best characterised actions of insulin combine to maintain postprandial plasma glucose at 5 mM. Following a meal increasing glucose levels promote insulin secretion from pancreatic beta cells. Insulin targets liver, muscle and adipose to alter glucose uptake, glycogen synthesis and glucose production, as well as lipid, fatty acid and protein metabolism, promoting storage of the incoming nutrients as glycogen, protein and fat. This continues until plasma glucose returns to 5 mM and insulin secretion is switched off. Not only does this generate fuel supplies for periods of prolonged fasting but it also prevents the deleterious effects of hyperglycaemia and hyperlipidaemia.

4. Insulin signalling in the periphery

Insulin action requires induction of a signalling network of molecules that connects the insulin receptor (IR) to the various proteins required to control metabolism (Fig. 1). The insulin receptor consists of a tetramer (2x alpha and 2x beta subunits generated from two distinct gene products). Insulin binds to the extracellular face of the receptor, inducing a conformational change that promotes activation of an intrinsic tyrosine kinase activity within the intracellular domain of the receptor, leading to autophosphorylation of the β-subunit of the IR. IRS proteins are recruited to the plasma membrane through an interaction with the phosphorylated IR, and these also become phosphorylated by the receptor on tyrosine residues [15]. This promotes recruitment of additional signalling proteins to the complex. For example, the lipid kinase phophatidylinositol (PI) 3-kinase which converts phosphoinositol-4,5-bisphosphate (PIP2) to phosphoinositol-3,4,5-trisphosphate (PIP3). This second messenger then attracts more proteins (including pleckstrin homology (PH) domain containing proteins) to the membrane, inducing co-localisation of enzymes and substrates, and activating protein kinase cascades (Fig. 1). The best characterised of these is the phosphoinositide dependent protein kinase (PDK1) pathway. PDK1 is a master regulator of a number of protein kinases, including protein kinase B (PKB, also known as Akt), PKC, p90 RSK, p70 S6K and SGK (see [16] for review). These protein kinases then phosphorylate and regulate a wide variety of proteins involved in metabolism. For example, PKB phosphorylates and inactivates GSK3 [17], and FOXO transcription factors [18]. These actions are involved in the proper regulation of hepatic gene transcription by insulin [19]. In addition, the inhibition of GSK3 by PKB modulates insulin induction of glycogen synthesis in muscle [20], while the activation of PKB is also required for insulin induction of glucose uptake into muscle [21]. PKB regulates the activity of mTOR, an intracellular nutrient sensor that is part of the pathway that controls protein synthesis [22]. Thus, the IRS/PI 3-kinase/PDK1/PKB pathway is considered a major pathway in the control of the metabolic actions of insulin.

A second major pathway downstream of the IRS proteins is the Ras-ERK pathway. Grb2/mSOS is a protein complex that interacts with phospho-IRS (at distinct phosphotyrosines to those that recruit PI 3-kinase). Once bound, mSOS exchanges GDP for GTP on the small G-protein Ras, thereby activating Ras. This promotes activation of c-Raf, which phosphorylates and activates MAP/ERK kinase (MEK), leading to phosphorylation and activation of ERK1/2 (Fig. 1). ERK1/2 has multiple cellular substrates, most of which are related to growth, hence this pathway is generally considered to be important in insulin regulation of cell growth, although this is almost certainly an oversimplification.

There are many other signalling proteins known to be regulated at some level by insulin, including Rab, PKCζ, CAP and GLUT4 (all involved in glucose transport), c-jun (gene transcription), PDE3b, hormone sensitive lipase and ATP citrate lyase (fat metabolism) and BAD (apoptosis).

Therefore the regulation of each of these pathways is a potential marker of insulin sensitivity. However many of these proteins are regulated by insulin in a tissue specific manner, and most are also regulated by alternative cell stimuli (in particular growth factors). *This means that care must be taken when analysing single points in these pathways, with assessment of the actual response to direct insulin application (preferably at more than one concentration) being vital when attempting to quantify a true change in insulin sensitivity.*

5. Insulin and the blood–brain barrier

Insulin enters the CNS by crossing the blood–brain barrier in a regulated and saturable fashion [23]. The specific receptor/transporter has not been identified but the transport appears to saturate at euglycaemic concentrations of insulin, and therefore chronic plasma hyperinsulinaemia may not promote parallel increases in insulin in the CNS. Indeed, acute induction of type 1 diabetes (streptozotocin injection of rodents), which reduces plasma insulin, enhanced the rate of insulin uptake into brain [24]. In addition there is evidence that prolonged hyperinsulinaemia (as would be present in early stages of T2DM) generates insulin deficiency in the CNS (see [25] for review). Conversely, hyperinsulinaemia in the periphery in insulin resistant individuals has been reported to promote hyperinsulinaemia in the CNS [26]. In complete contrast to the protective effects of physiologic levels of insulin, hyperinsulinaemia in culture can sensitise neurons to toxin and stress-induced insults [27]. Therefore it remains controversial whether neurons are insulin resistant, insulin deficient or are exposed to hyperinsulinaemia in T2DM, but clearly the design of therapeutics targeting insulin action requires this issue to be resolved.

6. Insulin action on cognition

Insulin receptors are found in many areas of the brain, and IR expression was increased in the hippocampal dentate gyrus and CA1 field following training of rodents on a spatial memory task [28]. This implies that neuronal insulin sensitivity could be enhanced during learning. In addition, insulin administration can have direct actions on memory. For example, i.c.v. administration of insulin to rats improved performance on a passive-avoidance task [29], and intranasal insulin improved some aspects of cognition in mice [30]. Meanwhile memory was improved in healthy humans, and in patients with memory impairments, by intranasal insulin application [31], and by i.v. administration of insulin [32,33].

Insulin resistance and impaired glucose tolerance are considered early warning signs (major risk factors) for the development of T2DM. Insulin resistance was associated with impaired verbal memory [34], while memory impairment and reduced hippocampal volume was observed in elderly individuals with impaired glucose tolerance [35]. These studies highlight the fact that cognitive deficits may be developing in the pre-diabetic condition, for some time prior to diagnosis of diabetes or the initiation of any treatments. However they remain observations needing mechanistic evidence to confirm insulin resistance is the cause of these associations.

Interestingly neuronal IR numbers are thought to decline with age [36]. Some believe that the accelerated cognitive decline in AD is related to a reduction of IR in the brain of AD patients (for review see [37]). However IR expression is not trivial to quantify in post-mortem tissue and there is evidence for [38,39] and against [36] this hypothesis. However this controversial observation has led to a suggestion that some forms of AD may be a 'type 3 diabetes' [39]. As mentioned above the diagnosis of diabetes is defined by plasma glucose, not by insulin sensitivity, and the cognitive impairments associated with metabolic abnormalities appear to occur in pre-diabetic conditions (i.e. with insulin resistance and impaired glucose tolerance rather than just diabetes). Therefore it seems to be rather inaccurate to label AD with defects in neuronal insulin action as a type of diabetes. In fact there is as yet little evidence that reduced IR expression even in the periphery is a cause of any major form of diabetes.

How insulin exerts its beneficial effects on the brain is not yet clear, however one proposal is that insulin induces glucose uptake and metabolism in specific neuronal populations. For example insulin administration to rats has been shown to increase cerebral glucose metabolism [40]. This could be through a similar mechanism found in muscle and adipose, namely the induction of membrane localisation of the glucose transporter GLUT4. This isoform is expressed in several areas of the brain including the hippocampus and cortex [41], however direct evidence for loss of insulin regulation of glucose uptake in the brain causing cognitive impairment is currently lacking, even in animals lacking a neuronal IR (see below). Recently a defect in control of neuronal cholesterol biosynthesis was observed in mice with insulin deficiency, and the deficits could be reversed by i.c.v. insulin administration. This suggests a direct regulation of cholesterol content by insulin in some areas of the brain [42]. In addition insulin may regulate the production of acetylcholine [43] and uptake of norepinephrine [44] in the brain, and also the expression of NMDA receptors at synaptic membranes [45]. Therefore there are many potential mechanisms by which insulin could directly affect neuronal activity, all requiring more detailed study.

7. Genetic deletion of the insulin receptor in the brain

To fully investigate the importance of insulin and insulin like growth factors (IGF)-1 action on the CNS a number of different approaches have been used to remove insulin or IGF1 receptors specifically in neurons. Neuronal specific insulin receptor knockout (NIRKO) mice were generated using nestin cre-mediated ablation [46]. Perhaps surprisingly, neuronal inactivation of the IR had no effect on brain development or neuronal survival. In addition the NIRKO mice had no deficit in spatial memory, long-term learning or brain glucose metabolism [47]. Instead, these mice exhibited hyperphagia, mild insulin-resistance, and enhanced sensitivity to diet-induced obesity, suggesting that CNS IR contributes to the regulation of whole body energy homeostasis. The NIRKO mice have relatively low basal PKB and GSK3 phosphorylation in the brain, at residues targeted by insulin to regulate their activity. This suggests that these residues may well be regulated by insulin in the brain and that loss of insulin action reduces basal activity of the pathway (resulting in higher GSK3 activity). Interestingly the NIRKO model had an impairment of the counter-regulatory response to hypoglycaemia, manifest in a reduced sympathoandrenal response when compared to littermate controls [48]. This blunted counter-regulatory response was related to alterations in glucose sensing in the ventromedial hypothalamus and arcuate nucleus (possibly due to reduced GLUT4 expression), although glucose uptake across all brain regions during a HEC was not impaired [49]. More recently, NIRKO mice were reported to have a deficit in IGF1-induced hyperthermia, a response mediated through the preoptic area of the hypothalamus to activate brown adipose tissue [50]. Insulin action on the brain is directly implicated in the regulation of white adipose tissue (WAT) lipolysis. Scherer et al. reported that insulin infusion into the mediobasal hypothalamus suppressed lipolysis, while increasing WAT lipogenic protein expression. Conversely, NIRKO mice display decreased WAT lipogenesis and unchecked lipolysis [51]. This implicates the IR in IGF1 action on the brain, the control of body temperature and whole body fat storage.

An alternative approach to classical gene knockout studies is to selectively downregulate the IR gene later in life, even in adult mice. Bruning and colleagues compared the phenotype of an inducible whole body IR deficient mouse with that of an inducible IR knockout restricted to peripheral tissues of adult mice [52]. The study was a direct comparison of the effects of peripheral versus whole body insulin resistance in the adult mouse, allowing assessment of the contribution of neuronal insulin resistance to whole body energy homeostasis. While deficiency in IR expression produced severe hyperinsulinaemia in both models, hyperglycaemia only developed when IR was lost from all tissues. Similarly, deficiency of IR in all tissues produced a greater reduction in WAT mass and severe hypoleptinaemia. Leptin replacement normalised glucose metabolism, indicating that alterations in glucose metabolism occur largely as a consequence of lipoathrophy following whole body IR deficiency. This data is consistent with the neuron specific deletion of IR, indicating that central insulin action plays an important role in regulating WAT mass and whole body glucose metabolism [52].

More acute depletion of IR can be achieved using antisense oligodeoxynucleotide or siRNA directed against the insulin receptor precursor protein introduced directly into the brain. Obici and colleagues generated a specific decrease in IR in the medial portion of the arcuate nucleus using antisense, resulting in hyperphagia and increased fat mass in the rats [53]. In addition, the ability of insulin to reduce hepatic glucose production was significantly blunted. Reduction of IR in the ventromedial hypothalamus using lentiviral infection of an siRNA resulted in a similar impairment of peripheral glucose metabolism [54]. These studies both point to a direct action of insulin on hypothalamic neurons to modulate hepatic glucose metabolism, however a previous study found that lentiviral IR siRNA injection into the third ventricle did not alter peripheral glucose metabolism but rather regulated body weight and fat mass [55].

The IR has also been selectively downregulated in specific neuronal subpopulations. For example, targeted inactivation of IR in steroidogenic factor-1 expressing neurons in the ventromedial hypothalamus revealed a role for these neurons in mediating insulin dependent alterations in diet-induced development of obesity [56]. Similarly, targeted inactivation of IR in pro-opiomelanocortin and agouti-related peptide (AgRP)-expressing neurons in the arcuate nucleus revealed that IR in AgRP-expressing neurons modulated hepatic glucose production during a HEC [57]. In addition, targeted inactivation of IR in tyrosine hydroxylase expressing dopaminergic midbrain neurons generated hyperphagia with concomitant increased weight and fat mass. This implicates the control of these specific neurons by insulin (and/or IGF1) in the normal regulation of food intake and energy homeostasis [58].

In summary, gene knockout or knockdown studies have highlighted key physiological roles for the neuronal IR, particularly in the hypothalamus, in the control of peripheral glucose and fat metabolism but potentially in more fundamental neuronal processes. However there is little evidence to date from neuronal IR knockout studies for a key role in learning and memory. In addition, as discussed below, the IR can complex with other receptors, hence simply deleting the IR could be altering sensitivity to more than insulin (e.g. IGF1). Therefore, although these studies are compelling and clearly demonstrate the importance of the IR in specific neurons, the evidence that insulin directly regulates the cognitive function of the brain is not as clear-cut. This requires specific assessment of post receptor signalling in neurons exposed to insulin and related peptides.

8. Neuronal insulin and IGF1 receptors and Alzheimer's disease

The studies on knockout mice have highlighted roles for neuronal insulin in the control of body weight and glucose homeostasis, with little evidence of cognitive deficits. However high fat feeding of mouse models of AD (which overexpress a mutant APP or PS1 leading to generation of amyloid pathology and premature death) exacerbates the behavioural and pathological phenotype [59,60]. Similarly crossing these AD models with mouse models of obesity and diabetes also worsens cognitive impairments [61]. This is consistent with the concept that the generation of insulin resistance (and subsequently T2DM) accelerates the progression of AD. However, when the Tg2576 AD model was crossed with the NIRKO mouse, or a mouse lacking the IGF1 receptor in neurons, there was no enhancement of the cognitive deficits of the Tg2576 mouse [62]. Indeed Tg2576 mice with reduced IGF1 signalling in the brain were actually protected from the premature death associated with this model of familial AD (as well as having some reduction in amyloid production) [63]. Deletion of the IR from the neurons of this same mouse model of AD had even greater benefits on development of amyloid pathology yet did not counter the premature death of the model [62]. This clearly demonstrates different effects of the insulin and IGF1 signalling processes on amyloid pathology and premature mortality but questions the role of insulin and IGF1 in the cognitive deficits of these mouse models. The detrimental effects of high fat feeding on the Tg2576 and Triple Tg models, along with our own studies demonstrating that high fat feeding promotes a very specific cognitive deficit in rats [64], clearly suggest there is an effect of poor diet on neuroendocrine or metabolic function that influences behaviour. However whether this is due to a direct loss of insulin action on the brain (or an alternative diet induced change such as leptin or incretin resistance) requires further investigation.

9. Defective insulin signalling in Alzheimer's disease

It appears that all of the components of the insulin-signalling cascade are present within the CNS; however direct evidence that insulin actually regulates key neuronal functions through the same pathways across all brain regions as it does in the periphery is comparatively weak. Insulin is a member of a small family of polypeptides that includes (IGF)-1 and -2. The IR has high homology with the IGF1 receptor and indeed each receptor will bind and respond to both hormones although with an order of magnitude greater affinity for the cognate hormone. In addition the IGF1 receptor and IR can form hybrid receptors. The hybrid receptor is much more responsive to IGF1 than to insulin, and it is estimated that the majority of IR subunits in the brain are within heterocomplexes with IGF1 receptors [65]. This situation may be even more complicated as recent evidence suggests that the IR forms complexes with other growth factor receptors, such as the hepatic growth factor (HGF) receptor in the liver [66]. In this case HGF is reported to modify the response of liver cells to insulin [66]. Therefore it is important to consider whether processes that promote insulin resistance in neurons would affect the response of cells to other growth factors and vice versa. For example, there is compelling evidence that IGF1 is necessary for normal brain function [67] and cognitive impairment is associated with an age-related decline in serum IGF1 levels in rodents [68]. Therefore, like insulin, it seems that IGF1 has key beneficial effects on neuronal function and survival. As insulin and IGF1 induce similar signalling pathways it is likely that a molecular problem that generates insulin resistance (although not yet characterised) could also alter IGF1 signalling in the brain, hence IGF1 resistance as well as insulin resistance in the brain could contribute to the association of T2DM and cognitive decline.

All of the above data together demonstrates that simply measuring IR expression in tissue is not an accurate approach to assess the insulin sensitivity of a tissue. Steen and colleagues found a significant reduction in many aspects (mRNA and protein

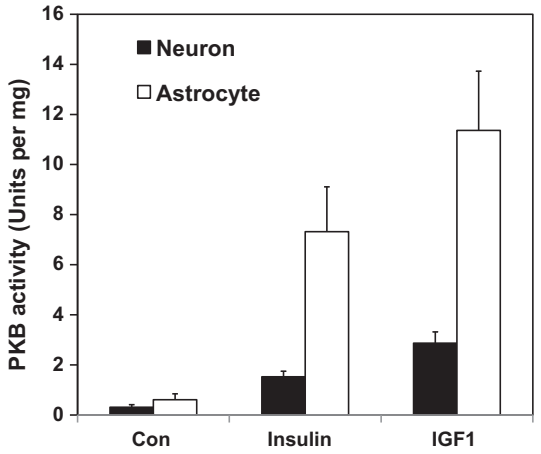

Fig. 3. Primary cells were incubated with insulin (100 nM) or IGF1 (100 ng/ml) for 15 min prior to lysis. PKB was immunoprecipitated from 100 μg of total cellular protein and incubated with crosstide and Mg[γ-^{32}P]ATP for 10 min. One unit of kinase activity is defined as that amount catalysing the incorporation of 1 nmol of phosphate into substrate in 1 h.

expression as well as post-translational modification) of the insulin/IGF signalling cascade in a number of brain regions associated with AD pathology when compared to control brain, although the amount of reduction varied from region to region [39]. Interestingly, there was no reduction in these transcripts in the cerebellum, a brain region relatively spared in AD pathology. More recent work investigated basal protein levels and post-translational modification (an indirect marker of activity) of the PI3K–PKB signalling pathway (Fig. 1) in tissue from AD, T2DM, or AD with T2DM [69]. Although this was only a small study they found significant reductions in PDK1, PKB and GSK3β protein expression in T2DM in comparison to control, and PI3K/p85, PDK1, and PKB in AD brain compared to control. Interestingly, the deficits were generally more severe in the brains of individuals presenting with both AD and T2DM (reductions in IRβ, IRS1, PI3K/p85, PDK1, PKB and GSK3β). These reductions in protein correlated with increased tau phosphorylation, down-regulation of O-GlcNAcylation of tau and enhanced calpain-I activation. Although correlative, these preliminary data would suggest that common pathological mechanisms occur in both T2DM and AD, and together they may produce a more severe phenotype. However it may be dangerous to extrapolate expression levels of signalling molecules to actual cellular sensitivity to a specific hormone. All of the studies to date examining insulin signalling in brain from AD patients have focused on basal signalling status compared to age-matched controls (due to the technical difficulty in obtaining samples before and after insulin exposure). As mentioned earlier, all of the proteins of the PI3K–PKB pathway (including the IR itself) can be regulated by agents other than insulin. Therefore the basal expression and activity of the pathway technically does not provide specific assessment of insulin sensitivity of the tissue (e.g. IGF1 induces the PKB pathway greater than insulin in neurons (Fig. 3)). In addition isolated brain tissue contains more than neurons. Indeed isolated astrocytes not only contain insulin (and IGF1) receptors but also induce the PI3K–PKB pathway to a greater extent in response to physiological insulin or IGF1 (Fig. 3). Finally, the absolute level of expression of components of a pathway does not always directly correlate with sensitivity of downstream targets of the pathway to stimulation. For example, only 5% of maximal PKB activation by insulin is required in liver cells to fully repress the insulin target gene phosphoenolpyruvatecarboxykinase [70], therefore this action of insulin can withstand a loss of most of the cellular PKB without losing sensitivity to insulin, yet requires PKB for response to insulin. Therefore new technology is required to quantitatively assess key neuronal processes regulated by insulin (before and after exposure to insulin at increasing concentrations, or specific actions of insulin). Only then will it be possible to fully assess the status of neuronal insulin sensitivity in models of AD or in human AD brain.

Amyloid β (Aβ) peptides are reported to regulate insulin signalling in the brain. Soluble Abeta reduces insulin's ability to induce the PI3K–PKB pathway in cultured hippocampal neurons [71], while soluble Aβ oligomers reduce plasma membrane IR in primary hippocampal neurons, promoting synaptic spine loss [72]. In both cases pretreatment with insulin protected against the action of Aβ suggesting a direct competition at the IR. It will be interesting to determine if this is confirmed in intact tissue and in vivo.

Insulin can enhance survival of HT22 neuronal cultures through a PI3K-mediated modulation of PKCdelta alternative splicing [30]. Insulin protects retinal neurons from stress-induced apoptosis, possibly via the PI3K–PKB pathway [73] or the mTOR–p70S6K pathway [74], both pathways harnessed by IGF1 and leptin receptors as well. Therefore loss of neuronal responsiveness to insulin, or insulin deficiency in the T2DM CNS, could render neurons more susceptible to neurotoxic insults (e.g. Aβ or inflammation in AD), leading to decreased survival of neurons in key areas of the brain associated with neurodegeneration in dementia.

The insulin-degrading enzyme (IDE) is a metalloprotease that catabolises insulin and Aβ, and may play a critical role in Aβ clearance in brain [75]. Insulin can regulate IDE expression and may directly compete with Aβ for binding to IDE. Mice lacking IDE have lower rates of Aβ and insulin degradation and develop hyperinsulinaemia and accumulate Aβ species in the brain [76]. These data together propose that insulin deficiency in the CNS could enhance Aβ accumulation through loss of insulin inhibition of IDE expression and reduced competition for IDE binding.

Finally, many of the protein kinases that can phosphorylate tau on residues known to exhibit increased phosphorylation in AD are regulated by insulin. The best example is GSK3, which phosphorylates tau on several residues [77,78]. This enzyme is regulated by insulin through the PI3K–PKB pathway in muscle cells [17], but it should be kept in mind that GSK3 is regulated by many agents using other signalling pathways.

10. Loss of metabolic control and cognition

Loss of insulin action on the brain is not the only mechanism by which dementia can be linked to diabetes. There is evidence that simple short-term alterations in glycaemic control may affect cognitive performance. Two large clinical trials reported an association between deficits in motor speed and psychomotor efficiency and mean glycated haemoglobin concentrations (an assessment of glucose control) in people with type 1 diabetes [79,80]. In addition cognitive impairments have been reported in T2DM associated with single measures of glycated haemoglobin [81]. It is possible that long-term hyperglycaemia may alter microvascular structure in the brain leading to the development of cognitive impairment. Meanwhile deliberate acute elevation of blood glucose induced specific decrements in working memory, attention and mood (although this was in people already diagnosed with T2DM) [82]. This may suggest that a more acute alteration in cerebral blood flow or osmotic effects on the brain may promote impaired cognition in diabetes. In contrast others have reported that intensive glucose lowering regimens have little effect on cognitive measures [83], suggesting that improving glucose control alone may not be sufficient to reverse the effects of diabetes on dementia. It seems likely that the role of glycaemic

control and hormone responsiveness in cognition and neurodegeneration will be complex. Associations may well depend on other clinical features (e.g. inflammation, infection, steroids, body composition etc), as well as the precise measure of cognition and pathology.

11. Inflammation and cognition

Microglial activation and inflammation within the CNS are linked to a number of neuropathological conditions including AD and Parkinson's disease [84], and increasing levels of inflammatory cytokines, e.g. IL-1b and IL-6 can disrupt hippocampal synaptic plasticity and elements of spatial learning. Obesity induced peripheral insulin resistance is associated with a marked increase in the production of pro-inflammatory cytokines and plasma levels of free fatty acids. Indeed chronic activation of the innate immune system in response to stress such as excessive or inappropriate fat deposition may contribute to the development of insulin resistance and T2DM [85]. Mice maintained on a diet rich in saturated fat for 16 weeks were found to be impaired in the Morris water maze, a test of spatial memory. Moreover, increased expression of various markers of neuroinflammation including TNF-a, IL-6 and the chemokine MCP-1 were observed in the brains of animals fed the high fat diet [86]. Therefore chronic inflammation could represent a common underlying condition promoting the association of AD with diabetes. Alternatively, hyperinsulinaemia associated with insulin resistance may promote CNS production of cytokines. Fishel et al. induced hyperinsulinaemia in healthy elderly men and observed a marked increase in the levels of pro-inflammatory cytokines (IL-1b. IL-6 and TNFa), F2-isoprostane, a brain derived marker of lipid peroxidation and Aβ42 within the cerebral spinal fluid [87]. Interestingly, those with the greatest BMI had the highest levels of TNFa, a cytokine that inhibits Abeta transport from the brain to the periphery. This may lead to a vicious cycle of increasing levels of TNFa and Abeta within the brain of obese hyperinsulinaemic individuals facilitating the formation of amyloid plaques. Furthermore, TNFa and IL-6 are known to induce activation of NFkB and subsequent transcription of the pro-inflammatory genes TNFa, IL-6 and IL-1b and the chemokines CRP and monocyte chemo-attractant protein-1. Thus induction of the innate immune system has the potential to have major implications on neural and cognitive function and worsening of pathology associated with AD.

Oxidative stress, the accumulation of advanced glycation end products (AGE) and the resulting CNS cellular and molecular damage may contribute to diabetes induced brain ageing [88]. The generation of AGE products increases pro-inflammatory mechanism within the brain that enhances oxidative stress and vice versa. The anti-oxidant capacity of the brain decreases with age but appears to decline faster in diabetes providing another mechanism by which diabetes could increase brain ageing leading to cognitive decline.

12. Perspectives for intervention in AD with insulin or insulin sensitising agents

Trials to improve insulin resistance or insufficiency in the CNS are only just starting. The main therapeutics available for treating insulin resistance include the biguanide metformin, the peroxisome proliferator activated receptor gamma (PPAR-γ) agonists and incretins. These are all being investigated for beneficial effects on cognitive performance in populations with diabetes and without.

The PPAR-γ agonists have been used in the treatment of T2DM for many years and are thought to improve insulin sensitivity through enhancing the deposition and function of adipose tissue, moving triglycerides and fatty acids away from liver and muscle, thereby improving response to insulin [89]. Interestingly induction of PPAR-γ activity may also reduce both Aβ accumulation and neuroinflammation [90,91]. Therefore PPAR-γ agonists have the potential to improve several molecular pathologies associated with both T2DM and AD making them potential therapeutics for the treatment of MCI associated with insulin resistance and neuroinflammation. Indeed the PPAR-γ agonist rosiglitazone protected the Tg2756 AD mouse model from corticosterone stress [92]. In addition, 6-month treatment with rosiglitazone improved attention and preserved memory in patients with amnestic mild cognitive impairment and early AD [93]. A correlation was observed between improvement in fasting plasma insulin and memory preservation, consistent with a mechanistic connection between insulin resistance and memory deficits. However a subsequent Phase III trial with rosiglitazone did not detect any benefit of the drug over placebo [94], while the recent evidence of increased heart failure associated with PPAR-γ agonists have reduced their use in diabetes therapy and may prevent further investigations of this class of insulin sensitising agent in dementia.

Metformin (in combination with weight control) remains the initial treatment of choice for T2DM, even though its precise mechanism of action remains unclear and controversial. It improves fasting insulin levels and enhances insulin regulation of hepatic glucose production. Therefore it is has always been considered an insulin sensitising agent, with its major actions on the liver. However more recent work has suggested it can cross the blood–brain barrier and regulate tau phosphorylation in a mouse model of AD [95]. Conversely it has been linked to enhanced amyloid production in cells [96]. However its insulin sensitising properties make it an ideal tool to establish the potential mechanistic link between insulin resistance and dementia, including AD, and as such several clinical trials are ongoing at the time of writing. A retrospective Taiwanese study provided the first epidemiological evidence that intervention with metformin could reduce the incidence of dementia in people with diabetes [97].

Glucagon-like peptide-1 and gastric inhibitory peptide are peptides made in the gut that induce insulin secretion from the pancreatic beta cells in a glucose dependent manner. Therefore they are technically insulin secretagogues rather than insulin sensitisers. Drugs that prevent degradation of these peptides (gliptins), or more stable forms of these peptides (exenatide and liraglutide) are now in clinical use as adjunct therapy in diabetes. Receptors for both peptides have been found in other areas of the body including the brain and additional biological actions are being discovered. Recently liraglutide and exenatide were found to antagonise processes linked to neurodegeneration and AD progression in mouse models, even in the absence of diabetes [98,99]. These incretins prevented the damaging effect of Aβ oligomers on CNS insulin signalling (in particular IRS1 regulation). This raises the exciting possibility that they could be a novel treatment for dementia irrespective of the presence of diabetes.

With some preliminary evidence that insulin may be reduced in AD brains (see earlier), studies are underway to investigate the therapeutic benefit of administration of insulin through the nose to patients with MCI and T2DM, bypassing any defects in blood–brain barrier insulin transport and the obvious concern of hypoglycaemia subsequent to peripheral administration [100]. Despite the disappointment of the human trials with rosiglitazone it remains quite possible that direct application of insulin to the CNS will have benefits even if the cognitive decline in the subjects is not due to insulin resistance. This approach plus the investigation of metformin therapy in patients with MCI remain worthwhile approaches in a condition with very few therapeutic options.

13. Summary

The relationship between insulin resistance and cognitive function is complex and while it is clear that insulin has important effects on neurobiology and potentially beneficial actions on neurodegenerative processes, there is still only indirect evidence that neurons (or astrocytes) develop defects in insulin action in line with peripheral insulin resistance. Although the epidemiological evidence that insulin resistance associates with cognitive impairments continues to accumulate most of the data remains correlative with little convincing detailed mechanistic proof that neuronal insulin resistance enhances the development of dementia. Indeed mouse knockout studies seem to suggest that the connection is not a simple loss of post-receptor signalling. We urgently require more accurate methodology to assess the insulin sensitivity of neuronal populations in vivo. This does not negate the importance of investigating whether insulin-sensitising drugs (or insulin itself) slow down cognitive decline in at risk groups, and we await the outcome of these trials with great hope. What is without doubt is the damaging effects of high fat diets and lifestyle on cognitive function and if this increase in 'New-Age' dementia is not addressed quickly there will be a health care crisis within a generation in most developed countries.

Acknowledgements

The work of the authors is supported by Alzheimer's Research UK and the Society for Endocrinology.

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