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Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes

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Abstract

Understanding of the role of insulin in the brain has gradually expanded, from initial conceptions of the brain as insulin-insensitive through identification of a role in regulation of feeding to recent demonstration of insulin as a key component of hippocampal memory processes. Conversely, systemic insulin resistance such as that seen in type 2 diabetes is associated with a range of cognitive and neural deficits. Here we review the evidence for insulin as a cognitive and neural modulator, including potential effector mechanisms, and examine the impact that type 2 diabetes has on these mechanisms in order to identify likely bases for the cognitive impairments seen in type 2 diabetic patients.

Keywords

insulin; hippocampus; diabetes; Alzheimer's; memory

For perhaps the past decade, it has been *de rigueur* to begin papers related to insulin and the brain with a note to the effect that 'contrary to previous dogma, insulin does indeed have effects on the brain.' This review will suggest that we have now moved beyond that point, such that a model of blood-borne insulin affecting the hypothalamus with regard to e.g. food intake and metabolic regulation is now itself dogma, but may need to be challenged or supplemented in (at least) two regards: the range of processes modulated by insulin and the location of insulin production. Specifically, we will suggest that cognitive deficits observed as a consequence of type 2 diabetes (T2DM) are likely due in large part to impaired central insulin Modulation of cognitive and metabolic processes in the hippocampus and beyond, and that insulin signaling is a critical component of, for example, memory processing. The question of whether, and (if so) to what extent, insulin is produced centrally is a complex one, and we review the history of this area briefly in Section 5 below, together with analysis of findings thus far; excellent recent reviews from Kyriaki Gerozissis (Gerozissis 2008; Gerozissis 2010; Gerozissis 2010) conclude (in contrast to conclusions drawn just a couple of years earlier; e.g. (Banks 2006)) that the evidence for significant synthesis of insulin within the adult mammalian brain is now convincing to the point of being overwhelming. We agree with that conclusion, which is consistent with the findings reviewed here and

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supports the importance of consideration of brain insulin signaling beyond regulation of metabolism.

The focus of this review is on type 2, rather than type 1 (T1), diabetes. Although important recent papers consider potential mechanisms in common between T1 and T2 diabetes (e.g. (Stranahan, Arumugam et al. 2008; Reagan 2011)), and the two conditions share some common features (hyperglycemia, if untreated, being the most common and defining characteristic), there are many important differences, reflected in quite distinct cognitive and physiological profiles (Craft 2009; Wrihten, Piroli et al. 2009; Reagan 2011); increased understanding of insulin's role within the brain supports the separation of the two conditions, and the effects of hyperglycemia *per se* are clearly distinct from those linked to insulin resistance (Gispen and Biessels 2000). Perhaps most importantly in the present context, the peripheral lack of insulin seen in T1DM may not be reflected in lowered brain insulin ((Stranahan, Arumugam et al. 2008); as might be expected if the brain is a source of insulin not reliant on pancreatic synthesis) and experimental induction of T1DM does not produce cognitive effects until several months after peripheral insulin production is impaired (Biessels, Kamal et al. 1996; Kamal, Biessels et al. 2000), suggesting that other factors (such as vascular effects, reduced brain glucose supply, altered glucocorticoid levels or many other possible effector mechanisms) may underlie cognitive changes in T1DM while brain insulin signalling may be at least relatively spared. Finally, the impact of T1DM on cognitive function in humans, as opposed to animal models, is small or absent in several studies (Group 1991; Group 1993; Jacobson, Musen et al. 2007; Kodl and Seaquist 2008; Wrihten, Piroli et al. 2009); even where present, the decline seen in T1DM is much slower than the effects of T2DM (Brands, Biessels et al. 2007), and may be due to nonspecific vascular and/or neurodegenerative effects, further arguing for separate evaluation of the two disease states. Hence, we shall focus here on brain insulin signaling and on T2DM, with the aim of determining whether alterations in brain insulin signaling may provide an explanation for the cognitive and neural effects of the disease.

As part of this special issue, the review is limited primarily to studies in animal models, both for reasons of space and to provide a tighter focus. Study of diabetes in human patients is complicated both by high variability between individuals and by confounding comorbidities, so that data from animal models may in fact provide a clearer basis for understanding as others have also suggested (e.g. (Reagan 2011)).

1. Insulin as cognitive modulator

One of the earliest suggestions that insulin might play an important role in cognitive processes – specifically, in hippocampal function – came from studies showing that training on a spatial memory task increased hippocampal insulin receptor expression (Zhao, Chen et al. 1999; Zhao, Chen et al. 2004), and the majority of work has continued to focus on the hippocampus, where insulin receptors are expressed at high levels; however, at least one early study also suggested a role for hypothalamic insulin as a regulator of memory processes, at least with regard to memory for food (Gerozissis, Rouch et al. 2001). Insulin receptors are also located in other brain regions involved in cognitive processes, notably the amygdala (Unger, McNeill et al. 1989; Unger, Moss et al. 1991; Abbott, Wells et al. 1999; Zhao and Akon 2001), but direct investigation of a role for insulin in cognitive processes outside the hippocampus has been limited.

The change in dogma with regard to actions of insulin in the brain, noted above, has been accompanied by a shift in thinking with regard to the potential for insulin to modulate cognitive processes. Ten years ago, a leading review ended with discussion of “the ambiguous role of insulin” [(Gispen and Biessels 2000), p 548] as a factor contributing to

the impact of diabetes on cognitive performance. In the interim, administration of exogenous insulin has been shown to enhance cognitive function when given i.c.v. (Park, Seeley et al. 2000; Haj-ali, Mohaddes et al. 2009), intranasally to a variety of human populations (Benedict, Hallschmid et al. 2004; Reger, Watson et al. 2006; Benedict, Hallschmid et al. 2007; Reger, Watson et al. 2008), and in large doses to the hippocampus (Moosavi, Naghdi et al. 2006; Babri, Badie et al. 2007; Moosavi, Naghdi et al. 2007; Moosavi, Naghdi et al. 2007); most recently, we showed that intrahippocampal delivery of physiological insulin doses acutely improved performance on a hippocampally-dependent spatial working memory task (McNay, Ong et al. 2010). More importantly, that study also demonstrated that specific blockade of intrahippocampal insulin produced a very large impairment of memory processing of the same magnitude as that produced by e.g. intrahippocampal administration of morphine (McNay and Gold 1998; McNay, Canal et al. 2006; McNay, Ong et al. 2010). Under identical conditions, we also showed that diet-induced insulin resistance, a rodent model of T2DM, both impaired memory performance and attenuated enhancement of performance by intrahippocampal insulin (McNay, Ong et al. 2010), as well as reducing hippocampal activity of the phosphatidylinositol-3-kinase (PI3K) signaling pathway, consistent with previous findings in obese rats (Winocur, Greenwood et al. 2005). Taken together with previous work, these data made clear that insulin plays a critical role in hippocampal memory processing and that systemic insulin resistance such as that seen in T2DM is accompanied by hippocampal insulin resistance also.

In passing we should note that mice with genetic deletion of neuronal insulin receptors have been reported to have only minimal cognitive effects, and little if any metabolic alteration (Schubert, Gautam et al. 2004). However, this apparently confusing result may be, at least in part, due to species differences between mice and humans/rats; we and others have been unable to demonstrate cognitive enhancement in mice following insulin administration, and there is data to suggest that insulin administration is associated with cognitive impairment in mice (Akanmu, Nwabudike et al. 2009), rather than enhancement, and may also have e.g. sedative effects; the basis for this possible disparity in findings between species requires further study. Interestingly, enhancement of insulin sensitivity in mouse models does appear to improve cognitive performance (Pedersen, McMillan et al. 2006), and cognitive performance in aged mice is linked to expression of insulin-related genes (Stranahan, Lee et al. 2010).

1.1 Specificity of insulin effects

A recent paper suggests that insulin-like growth factor 2 (IGF-2) may also play an important role in hippocampal memory processes (Chen, Stern et al. 2011). No insulin control was used in that study, but the possibility exists of cross-reactivity between insulin and insulin-like growth factors in Modulation of cognitive and other neural processes. However, insulin-like growth factor 1 (IGF-1) did not mimic the effects of insulin when given intrahippocampally (McNay, Ong et al. 2010), and specific blockade of insulin (using an antibody-like peptide without cross-reactivity for IGF-1 or -2) markedly impaired memory (McNay, Ong et al. 2010), supporting a specific role for insulin in hippocampal cognitive processing.

1.2 Cognitive impact of insulin resistance versus high-fat diet and/or obesity

Several lines of work have demonstrated that rodent models of diet-induced obesity, using a high-fat diet and/or fructose, lead to cognitive impairment (Greenwood and Winocur 1990; Greenwood and Winocur 2001; Greenwood and Winocur 2005; Winocur and Greenwood 2005; Winocur, Greenwood et al. 2005; Ross, Bartness et al. 2009). In general, it is assumed that the effects of such treatments may occur via impairment of central metabolism, but alterations in circulating lipids have also been noted as a potential factor (Ross, Bartness et

al. 2009); the two factors are likely linked, as circulating free fatty acids (FFAs) are directly linked to insulin resistance (Levin, Triscari et al. 1980; Cornier, Dabelea et al. 2008), and elevations in FFA lead to further insulin resistance. In contrast, a dietary increase in omega-3 and -6 fatty acids, as well as certain medium chain triglycerides, has been reported to improve cognitive performance, including memory (Auestad, Scott et al. 2003; Morris, Evans et al. 2003; Issa, Mojica et al. 2006; MacLean, Newberry et al. 2006; Arsenault, Julien et al. 2011). Surprisingly, the direct impact of fatty acids on hippocampal function has been little studied. Preliminary data from our lab (Cotero and McNay 2010) strongly support an effect of fatty acid type on both cognitive performance and hippocampal metabolism, with saturated fats impairing while unsaturated fats enhance both performance and metabolism; this effect would reward further study, but is consistent with an earlier report in mice using i.c.v. administration (Farr, Yamada et al. 2008). The fact that fatty acids, like insulin, are known to modulate neural activity in the hypothalamus (Oomura, Nakamura et al. 1975; Wang Cruciani-Guglielmacci et al. 2006), is further support for a potential direct action of FAs within e.g. the hippocampus. However, diabetogenic diets have been generally used as a model of T2DM rather than purely as a dietary manipulation. One study in which animals placed on a high-fat diet were divided into diet-obese and diet-resistant found that only those animals in which the diet produced insulin resistance and obesity showed any effect on cognitive performance or hippocampal metabolism (McNay, Ong et al. 2010), suggesting that the effects of such diets are via induction of impaired insulin sensitivity rather than being direct effects of the diet *per se*. A possible effect of insulin resistance in causing dyslipidemia should be kept in mind when considering potential effector mechanisms for insulin within the brain, below. Interestingly, FFAs may be important not only via direct effects, but also via involvement in the links between insulin resistance and abnormal accumulation of brain beta-amyloid protein (A β), discussed below (Craft 2009). As recently noted (Stranahan and Mattson 2011), although models of diabetes induced by a high-fat diet are perhaps the best current model of human T2DM, care needs to be taken in parsing the multiple possible effects of a high-fat diet; nonetheless, diet-induced insulin resistance in mice (Moroz, Tong et al. 2008), rats (Clegg Benoit et al. 2005; McNay, Ong et al. 2010) and hamsters (Mielke, Taghibiglou et al. 2005) produces similar impairment of central insulin signaling despite differences in both diet and species. In addition, recent data suggest that increased ceramide consumption may be one, and possibly a major, factor linking cognitive impairment in obesity with development of Alzheimer's disease ((de la Monte, Tong et al. 2010); see also Section 3.6 below).

2. Cognitive deficits in T2DM

Review of the specific details and limits of cognitive alterations accompanying T2DM has been comprehensively done elsewhere (e.g. (Biessels, Deary et al. 2008; Kodl and Seaquist 2008; van den Berg, Kloppenborg et al. 2009; van den Berg, Reijmer et al. 2010)), and is beyond the present scope; the existence of such deficits is well-established. However, a focus on the hippocampus as a site of insulin's actions in modulation of cognitive processes is supported by the clinical finding that cognitive deficits in human T2DM patients (and in patients with impaired insulin signaling even in the absence of T2DM; (Messier, Awad et al. 2004; Watson and Craft 2004)) tend to be greater on hippocampally-dependent tasks (Awad, Gagnon et al. 2004; Kodl and Seaquist 2008; Bruehl, Wolf et al. 2009); as the disease progresses and/or the patient ages, deficits are also seen in tasks mediated by other brain regions (Arvanitakis, Wilson et al. 2004; Akisaki, Sakurai et al. 2006), but their cause requires further study. The fact that insulin receptor expression is high in the hippocampus provides a likely explanation for the effects of insulin resistance being seen on hippocampally-dependent tasks: if the level of endogenous insulin signaling in Modulation of hippocampal cognitive processes is high at baseline, it has further to fall and hence there is a larger possible effect of insulin resistance.

3. Effector mechanisms of insulin within the brain: candidates for cognitive regulation

The largest section of this review will examine mechanisms by which insulin may be acting to regulate cognitive and neural processes, and the impact (if known) of T2DM on those mechanisms.

3.1 Insulin and metabolism

Perhaps the most intuitive mechanism for modulation of neural function by insulin is via regulation of glucose metabolism. The insulin-sensitive glucose transporter GluT4 co-localizes with insulin receptors in the brain (Vannucci, Koehler-Stec et al. 1998), and is reduced following induction of T2DM (Winocur, Greenwood et al. 2005); supply of glucose to the brain and especially to the hippocampus is well-established as a critical regulator of cognitive processes (Gold 1995; McNay, Fries et al. 2000; McNay and Gold 2001; McNay and Gold 2002; Gold 2005), and insulin has been shown to cause translocation of GluT4 to the cell surface of hippocampal neurons (Reagan 2005). Moreover, insulin has an inverted-U dose-response curve for enhancement of memory that resembles that seen with direct administration of glucose (Parsons and Gold 1992; Craft and Watson 2004; Watson and Craft 2004; Reger, Watson et al. 2008; McNay, Ong et al. 2010; McNay, Ong et al. 2010). The lack of whole-brain metabolic regulation by insulin was one of the cornerstones of the early perception of the brain as insulin-insensitive; however, several studies have shown that under certain conditions, insulin can indeed regulate neural metabolism and in particular, stimulates glucose uptake in the medial temporal lobe and hippocampus (Henneberg and Hoyer 1994; Hoyer, Muller et al. 1994; Hoyer, Henneberg et al. 1996; Bingham, Hopkins et al. 2002). Consistent with these findings, we found that insulin administration to the hippocampus causes a rapid and sustained increase in local glycolysis, but that this effect is completely attenuated in animals with T2DM (McNay, Ong et al. 2010). These data offer strong support for direct metabolic support of hippocampal cognitive processes by insulin, and a potentially simple basis for cognitive impairment seen in T2DM.

In the context of metabolic support, it is worth noting that the incidence of recurrent hypoglycemia (RH) following intense insulin therapy is increasing in T2DM patients (McNay and Cotero 2010). RH causes marked adaptations in brain glucose supply and usage but also in e.g. synaptic plasticity, leading to significant changes in cognitive performance (McNay and Sherwin 2004; McNay 2005; McNay, Williamson et al. 2006); while not a direct effect of T2DM, RH-induced changes may present a confound both in human studies and in animal models that require insulin treatment for viability. RH is commonly considered as a metabolic stressor, but chronic hyperglycemia may also be considered a stressor (Reagan 2011). RH has traditionally been considered to be a complication of T1DM, but the incidence in T2DM patients is increasing as intensive glucoregulatory therapies are more commonly used. Interestingly (and indicative of the inter-related nature of many of the central effects of insulin resistance), both RH and insulin resistance are linked to abnormal accumulation of brain A β , albeit via different mechanisms (Julien, Tremblay et al.; Ho, Qin et al. 2004; McNay, Green et al. 2010), supportive of the idea that lack of metabolic regulation in either direction – too much or too little fuel – may act to stress the brain and lead to negative consequences.

3.1.1 Vascular effects—Several studies note that insulin regulates not only neural function but also vascular supply. Because insulin resistance may lead to vasoconstriction, this would provide a second mechanism linking T2DM with impairments of glucose supply to the brain and specifically the hippocampus (Craft 2009). A metabolic effector mechanism for insulin would also provide a potential explanation for impact being seen on hippocampal

processes: in addition to a high density of insulin receptors, the hippocampus is known to be especially sensitive to perturbations in glucose supply (Gold 1995; McNay, Fries et al. 2000; McNay and Gold 2002; Piroli, Grillo et al. 2002; Canal, Stutz et al. 2005). This suggestion would also be consistent with an apparent worsening of the impact of T2DM with age, as metabolic regulation and control of glucose supply to the brain are adversely affected by aging (Korol and Gold 1998; McNay and Gold 1999; McNay and Gold 2001; Gold 2005) and vascular function may be impaired (Craft 2009). The impact of vascular impairment can be difficult to distinguish from that of diabetes, and also from e.g. accumulation of A β , a further difficulty in accurate analysis of human studies (Craft 2009). One aspect of vascular change with T2DM – the potential for impaired transport of insulin across the blood-brain barrier (Craft, Peskind et al. 1998; Zhao and Townsend 2009) – may not be as significant as originally thought, in the context of insulin being produced within the brain rather than solely delivered from the bloodstream.

3.2 Insulin signaling pathways

Brain insulin receptors are similar to those expressed peripherally (Wozniak, Rydzewski et al. 1993), and as in the hypothalamus and periphery, insulin appears to act within the hippocampus via activation of the PI3K signaling pathway, consistent with e.g. a role in translocation of GluT4 which is indeed seen *in vivo* (Grillo, Piroli et al. 2009). However, this same signaling pathway also appears to underlie insulin's effects on synaptic activity, discussed below, via modulation of e.g. GABA channels (Vetiska, Ahmadian et al. 2007). In general, the literature has focused on PI3K as the likely signaling pathway for insulin's actions within the brain. However, other mechanisms exist and are likely important. To give two examples: firstly, insulin is known to directly affect ATP-gated potassium channels (K_{ATP} ; (Spanswick, Smith et al. 2000; Pocai, Lam et al. 2005)) and has impaired ability to open these channels (and hence modulate neural firing) in the hypothalamus of insulin-resistant animals (Spanswick, Smith et al. 2000). Modulation of K_{ATP} channels within the hippocampus has been shown to impact memory performance (Stefani and Gold 2001), so that insulin is likely able to regulate hippocampal activity at least in part via this pathway independent of, or interacting with, effects on PI3K and/or metabolism. Secondly, there is substantial evidence that insulin may act, in the brain, via mitogen-activated protein kinase (MAPK; (Huang Lee et al. 2004; de la Monte and Wands 2005; van der Heide, Kamal et al. 2005; O'Malley and Harvey 2007; Gerozissis 2010)), although this pathway appears to have been little studied in the context of cognitive performance or insulin resistance.

3.3 Insulin as synaptic modulator

As noted above, insulin can act to modulate neuronal firing via actions at K_{ATP} channels; in addition, there is a large body of work showing that insulin can alter synaptic plasticity, affecting both long-term potentiation (LTP) and depression (LTD). Insulin acts to cause LTD by removing AMPA channels from the synaptic membrane (Lin, Ju et al. 2000; Man, Lin et al. 2000; Ahmadian, Ju et al. 2004), with effects including alteration of the rate of endocytosis and recycling in a subtype-specific manner, but can also promote LTP by altering the stimulation frequency-response curve for induction of LTP ((van der Heide, Kamal et al. 2005); this topic has been comprehensively reviewed (Zhao and Townsend 2009)). These studies also showed a role for modulation of NMDA channels in insulin's effects, in addition to regulation of AMPA channels (Skeberdis, Lan et al. 2001). Further complicating the picture, insulin can also regulate translocation of GABA receptors to the plasma membrane (a mechanism that provides a further link back to glucose's effects on cognitive performance and hippocampal function, which have been suggested to be via modulation of GABAergic activity (Degroot, Kornecook et al. 2003; Shah and Parent 2003; Erickson, Watts et al. 2006)), so that both excitatory and inhibitory acute neurotransmission as well as long-term plasticity are potentially under the direct regulation of insulin. The

interaction between insulin's synaptic plasticity effects and diabetes have been primarily demonstrated in the context of streptozotocin-administered rodents, a model of T1DM, where a significant deficit in LTP is observed (Biessels, Kamal et al. 1996; Biessels, Kamal et al. 1998; Izumi, Yamada et al. 2003; Stranahan, Arumugam et al. 2008). In contrast, models of T2DM have shown less consistent results ((Gerges, Aleisa et al. 2003; Belanger, Lavoie et al. 2004; Stranahan, Arumugam et al. 2008), reviewed in (Reagan 2011)). The fact that insulin resistance causes deficits in short-term and working memory, and insulin administration can rapidly enhance working memory (McNay, Ong et al. 2010), combined with the variation in long-term plasticity seen in models of T2DM, perhaps suggests that alterations in plasticity may not be the primary mechanism underlying cognitive deficits in T2DM. However, much of the data in this area has thus far been obtained *in vitro*, and there is a clear need for *in vivo* studies of both plasticity and acute neurotransmission, perhaps using microdialysis in the hippocampus of awake animals performing a hippocampally-dependent task, to provide clear data on the impact of insulin and insulin resistance on synaptic activity.

3.4 Insulin and glucocorticoids

The concept of diabetes as a metabolic stressor was noted above; recently it has been suggested that some or all of the cognitive effects of diabetes may be mediated not directly through insulin signaling but via alterations in glucocorticoid levels (GCs; (Stranahan, Arumugam et al. 2008; Stranahan, Lee et al. 2008; Stranahan, Arumugam et al. 2010; Reagan 2011)); in particular, one study suggested that impaired GC regulation might underlie cognitive deficits associated with both T1DM and T2DM (Stranahan, Arumugam et al. 2008). GCs are well-established to modulate cognitive functions including hippocampal memory processes (Quirarte, Roozendaal et al. 1997; de Quervain, Roozendaal et al. 1998; McGaugh and Roozendaal 2002; Roozendaal 2002; Roozendaal, McEwen et al. 2009), with acute elevation generally enhancing memory while chronic elevation leads to hippocampal damage, including cell loss, and cognitive impairment (Gould, Woolley et al. 1991; McEwen, Magarinos et al. 2002; Lupien, McEwen et al. 2009; Roozendaal, McEwen et al. 2009). Moreover, GCs and insulin act in opposite directions in modulation of e.g. hippocampal GluT4 (Piroli, Grillo et al. 2007), so that insulin resistance might well interact with GC signaling; indeed, removal of adrenal steroids increases sensitivity to central insulin (Chavez, Seeley et al. 1997), suggesting a bidirectional modulation of neural function. GCs have been suggested as a potential causal agent for conditions including Alzheimer's disease, associated with impaired insulin signaling (Dhikav and Anand 2007), and cause impaired neuronal and glial glucose usage (Sapolsky 1986; Brunetti, Fulham et al. 1998; Gip, Hagiwara et al. 2004) whereas damage caused by elevation of GCs can be reversed by supplying additional fuel (Sapolsky 1986). Moreover, GCs have multiple deleterious effects in the hippocampus, including interference with neurogenesis, and neurogenesis is associated with enhanced memory performance but impaired in T2DM (Gould, Beylin et al. 1999; Drapeau, Mayo et al. 2003; Cao, Jiao et al. 2004; Aimone, Wiles et al. 2006; Lindqvist, Mohapel et al. 2006; Ramirez-Amaya, Marrone et al. 2006; Dupret, Revest et al. 2008; Fontan-Lozano, Lopez-Luch et al. 2008; Lafenêtre, Leske et al. 2009; Lang, Yan et al. 2009; Stangl and Thuret 2009; Deng, Aimone et al. 2010; van der Borgh, Kohnke et al. 2011), further suggesting a possible role for GCs in the etiology of cognitive deficits associated with insulin resistance. However, the exact contribution of GC effects to the cognitive impairments seen in T2DM remains to be determined; experimental manipulations commonly ablate epinephrine release in addition to GCs, presenting one potential confound given the role of epinephrine as a cognitive regulator (Williams and McGaugh 1993; Gold 1995; Ramakrishnan and Namasivayam 1995; Korol and Gold 1998; McGaugh and Roozendaal 2002), and measurements of e.g. glucose metabolism remain to be performed in order to fully understand the role of GCs in linking insulin resistance with cognitive

impairment. The fact that GCs are elevated in both T1DM and T2DM, whereas cognitive deficits are seen predominantly in patients with T2DM, may also pose a challenge for this mechanism as a primary mediator of cognitive impairment.

3.5 Insulin and neurogenesis

Intriguingly, insulin receptor expression is high in both areas of the brain – hippocampus and olfactory bulb – that show relatively high levels of adult neurogenesis. As noted above, neurogenesis is linked to hippocampal memory processing and appears to be impaired in T2DM. Moreover, insulin resistance is associated with conditions such as depression that are linked to impaired neurogenesis (Malberg, Eisch et al. 2000; McEwen, Magarinos et al. 2002; Awad, Gagnon et al. 2004; Ernst, Olson et al. 2006; Becker and Wojtowicz 2007; Gerozissis 2010; Reagan 2011), possibly linked via modulation of serotonergic activity (Gerozissis 2010). Given that insulin is a growth factor, and that insulin-like growth factor 1 (IGF-1) is established as a regulator of hippocampal neurogenesis (Aberg, Aberg et al. 2000; Anderson, Aberg et al. 2002; Aberg, Aberg et al. 2003; Dempsey, Sailor et al. 2003; Bateman and McNeill 2006; Ding, Vaynman et al. 2006; Aberg Johansson et al. 2007; Annenkov 2009), it is natural to suggest that insulin signaling within the hippocampus might directly regulate both neurogenesis and memory processing. We are currently investigating this possibility, and very preliminary results (A. Recknagel, E. Burton & E.C. McNay, unpublished data) suggest that indeed, neurogenesis patterns are altered by insulin resistance and/or administration in ways that directly correlate with spatial memory performance.

3.6 Insulin and beta-amyloid

Links between insulin and A β within the brain have been the subject of increasing investigation over the past two decades, as the fact of significant comorbidity between T2DM and Alzheimer's disease (AD) has become more established (Leibson, Rocca et al. 1997; Steen, Terry et al. 2005; Brands, Biessels et al. 2007; van den Berg, Kloppenborg et al. 2009); but see also the possibility that obesity *per se*, perhaps linked to ceramide consumption, may be more directly linked to AD than is T2DM (de la Monte, Tong et al. 2010).. A β processing within the brain is known to be impaired in T2DM (Janson, Laedtke et al. 2004); not only does insulin compete with A β for degradation, as both peptides are cleaved by the same protease (insulin-degrading enzyme, IDE; (Chesneau, Perlman et al. 1997; Bernstein, Ansorge et al. 1999; Gasparini, Gouras et al. 2001; Cook, Leverenz et al. 2003; Farris, Mansourian et al. 2003; Morelli, Llovera et al. 2004; Zhao, Teter et al. 2004; Zhao, Lacor et al. 2009)) but insulin also modulates removal of A β (Gasparini, Gouras et al. 2001; Gasparini, Netzer et al. 2002; Wei Qiao and Marshal 2006) and may directly prevent pathogenic A β binding (De Felice, Vieira et al. 2009) as well as being able to reverse cognitive deficits and reduce amyloid load in AD patients (Reger, Watson et al. 2006; Reger, Watson et al. 2008). Moreover, insulin-amyloid interaction is bidirectional: A β may affect brain function via downregulation of insulin signaling (Zhao, De Felice et al. 2008), following direct binding to insulin receptors and downregulation of PI3K signaling (Townsend, Mehta et al. 2007). The links between the two diseases have become sufficiently strong for AD to be described as a form of neural diabetes (Steen, Terry et al. 2005; de la Monte and Wands 2008). Several good reviews have covered these links in detail from a variety of perspectives (Craft, Peskind et al. 1998; Frolich, Blum-Degen et al. 1998; Luchsinger, Tang et al. 2001; Gasparini, Netzer et al. 2002; Arvanitakis, Wilson et al. 2004; Carro and Torres-Aleman 2004; Schubert, Gautam et al. 2004; Steen, Terry et al. 2005; Sun and Alkon 2006; de la Monte and Wands 2008; Neumann, Rojo et al. 2008; de la Monte 2009; Laron 2009; Liao and Xu 2009; Zhao and Townsend 2009); taken together, the data are now overwhelming that a common factor in the cognitive deficits in both T2DM and AD is an impairment to brain insulin signaling. Moreover, because elevations in insulin lead to accumulation of A β which then further impairs insulin signaling impairment to brain

insulin signaling can initiate a vicious spiral of decline in brain metabolism, synaptic function, and cognitive impairment; a similar suggestion has recently been made by others (Zhao and Townsend 2009). Amyloid and insulin share common targets, always in opposition: for instance, A β accumulation is correlated with neural hypometabolism (Cohen, Zolko et al. 2008). Further, AD is well-known to have earliest and most severe consequences in the hippocampus, showing a commonality with insulin in site of action as well as mechanism. It should be noted that the toxic effects of A β accumulation appear to be linked to the oligomeric form, with monomeric A β being if anything neuroprotective via activation of PI3K (Giuffrida, Caraci et al. 2009); the details of this mechanism remain to be elucidated, but insulin may act to protect against amyloid toxicity not only by supporting metabolic and neuronal function, but also by preventing oligomerisation (Lee, Kuo et al. 2009), impairment of which will be a further deleterious effect of insulin resistance.

The literature on AD and T2DM is voluminous, such that a full review is not possible here. However, the overall conclusion is that a strong candidate for a mechanism underlying cognitive deficits in both T2DM and AD is impaired central insulin signaling leading to toxic accumulation of oligomeric A β , which then impairs glucose supply and synaptic function by inhibiting insulin signaling. The fact that the risk of AD developing from T2DM is greatest when T2DM patients receive exogenous insulin as therapy (Ott, Stolk et al. 1999) is further support for this causal chain, and it has been suggested that hyperinsulinemia may be in part caused by an endogenous mechanism aimed at increasing insulin-stimulated amyloid removal and degradation (Watson and Craft 2003; Watson and Craft 2004). In the AD brain, insulin resistance is caused by A β accumulation even in the absence of systemic hyperinsulinemia (Zhao and Townsend 2009), so that brain insulin resistance may precede and perhaps cause T2DM in some cases, rather than the opposite. The two diseases exacerbate each others pathologies, and appear to share a set of common molecular bases, so that many or most of the sections above – on metabolism, synaptic function, and vascular effects (Craft 2009), for example – could be considered not only as mechanisms mediating the effects of insulin resistance directly, but also as targets for amyloid-mediated impairment. Overall, the effects of insulin resistance on toxic amyloid accumulation may be as deleterious or worse for cognitive and hippocampal function than the direct effects.

4. Conclusions

The data are now overwhelming that insulin can act to modulate cognitive processes, especially those within the hippocampus, and that insulin resistance such as that characterizing T2DM is associated with cognitive deficits; the data presented here strongly suggest that systemic insulin resistance is accompanied by central insulin resistance, and that such impaired insulin signaling is the causal mechanism underlying cognitive impairment. Importantly, recent work has conclusively shown that endogenous intrahippocampal insulin is a key component of memory processes, and that acute blockade of hippocampal insulin signaling produces profound cognitive deficits, supporting the physiological role of insulin as a hippocampal modulator.

There are several potential mechanisms by which insulin and insulin resistance have been suggested to regulate cognitive processes, most commonly within the hippocampus; a role in regulation of glucose metabolism is perhaps the best-supported, but several other mechanisms – most notably interactions with beta-amyloid – are becoming increasingly well-established. Such mechanisms are not mutually exclusive, of course, and the challenge remaining is both to understand the interactions between potential mechanisms and to transfer knowledge gained in animal models into therapies for human patients.

5. Addendum: Is insulin made in the brain?

5.1. History

At the time insulin was first detected in the brain of dogs (Margolis and Atsuer 1967) the pancreas was the only known source of insulin. Controversy over the possibility that insulin might also be centrally generated developed following some initial reports of high concentrations in rat brain, suggesting that it was either collected or synthesized in brain tissue (Havrankova, Schmechel et al. 1978). However, improved extraction techniques and immunoassays soon revealed that insulin concentrations in the brain are typically a fraction of that found in the blood (Eng and Yalow 1981). Measurement of low brain insulin protein levels, and initial failure to detect proinsulin messenger RNA in the brain, supported the classical assumption that insulin is not synthesized in the brain (Yalow and Eng 1983). However, central and peripheral sources of insulin are not mutually exclusive, and over the years substantial evidence has accumulated for the possibility that the brain might in fact be a second source of insulin (reviewed by (Plata-Salaman 1991; Wozniak, Rydzewski et al. 1993; Gerozissis 2003; Gerozissis 2010)). This question remains controversial, and readers' analysis of the present review may perhaps be aided by a brief critical discussion of the evidence.

5.2. Evidence for a peripheral origin of central insulin

The widely held, and perhaps to some extent *a priori*, assumption that insulin detected in the CNS was of pancreatic origin contributed, it seems possible, to the initial conclusion of many researchers that circulating blood-born insulin must enter the brain given that insulin was present within the brain. Several experiments attempted to measure the influx of insulin across the blood-brain barrier (BBB) or blood-cerebrospinal fluid barrier, and/or to detect the expected transport mechanism. Early studies investigated the relationship between blood and cerebrospinal fluid (CSF) insulin levels; the first report of insulin in dog CSF reported that the concentration was consistently around 25% of blood (Margolis and Atsuer 1967), but subsequent studies had widely varying results. A decade later, experiments in dog measured a small rise in CSF insulin after peripheral infusion of exogenous insulin (Woods and Porte 1977), and suggested that changes in the two concentrations were temporally linked; conversely, around the same time a study using labeled insulin failed to find uptake in rat hypothalamus (Goodner and Berrie 1977). In a similar set of conflicting studies, no change in CSF insulin levels was seen by one group levels after a physiological increase in plasma insulin that was induced by glucose infusion (Ono, Steffens et al. 1983), but using nearly identical methods, a delayed rise in CSF insulin after peripheral glucose infusion was later seen (Steffens, Scheurink et al. 1988). Findings in clinical studies were likewise rather varied: for instance, no correlation was observed between blood and CSF samples from 81 human subjects (Reiser, Lenz et al. 1985), but a slow rise in CSF insulin was detected in humans after peripheral insulin infusion with glucose clamp (Wallum, Taborsky et al. 1987). Overall, a consensus developed that insulin could be transported from blood to brain; perhaps the most direct evidence came from work using neonatal rabbits, a system in which degradation of the radiolabeled tracers is reduced in comparison with adult animals, and in which thaw-mount autoradiography shortly after peripheral insulin infusion showed silver grains in pericapillary spaces and brain tissue (Duffy and Pardridge 1987). The fact that insulin receptors were found in high concentrations within specific brain regions further supported the idea that insulin must be acting within the CNS, a concept that was itself an advance from early dogma of the brain as an insulin-insensitive organ (based largely on whole-brain glucose uptake and metabolism measurements that consistently showed little effect of insulin on total cerebral glucose metabolism, a result that has been replicated by recent MRS and PET studies of the cerebral cortex (Hasselbalch, Knudsen et al. 1999; Seaquist, Damberg et al. 2001); but see also (Bingham, Hopkins et al. 2002)).

5.2.1. Development of an insulin blood-to-brain transport model—Based on the above work, a theory emerged for receptor-mediated transcytosis of insulin across the brain capillaries (Pardridge 1986). Evidence of insulin binding to isolated human (Pardridge, Eisenberg et al. 1985) and internalization in neonatal rabbit (Frank, Jankovic-Vokes et al. 1985) brain microvessels formed the basis for an *in vitro* model of BBB transport. This work was supported by work with a tissue culture model of peripheral blood vessels that claimed receptor-mediated transport of insulin across bovine endothelial cells (King and Johnson 1985). Building on this work and mode, infusion experiments in dog investigated the specificity and kinetics of insulin transport from blood to CSF (Schwartz, Sipols et al. 1990; Schwartz, Bergman et al. 1991; Baura, Foster et al. 1993). This work produced a model of saturable insulin delivery through an intermediate compartment that was hypothesized to be brain interstitial fluid. Further studies with a mouse model of brain transport after capillary depletion (Triguero, Buciak et al. 1990) measured the accumulation of radio-labeled insulin tracer or species specific insulin isoforms (Banks, Jaspan et al. 1997; Banks, Jaspan et al. 1997; Banks, Jaspan et al. 1997; Banks and Kastin 1998).

5.2.2. Potential limitations to the blood-to-brain model—The model proposed by Banks, Pardridge and colleagues gained wide acceptance, but aspects of the supporting data may have potential weaknesses; although in-depth discussion is beyond the scope of this review, we note some of the key elements. Some early results based on tissue culture and microvessel isolation may have lacked sufficient precision to form the basis for firm conclusions, and some such results were later challenged, sometimes as part of a challenge to the underlying model (Pardridge 1986; Steil, Ader et al. 1996; Hamilton-Wessler, Ader et al. 2002). BBB permeability and brain uptake calculations that assume negligible binding and degradation of the tracer molecule may be inappropriate for insulin, and the kinetics of insulin binding and internalization may also pose issues for methods based on e.g. vascular space markers, or perfusion to cause presumed clearance of any blood-borne insulin. Much of the data supporting the proposed model may have been interpreted in light of an underlying *assumption* of insulin binding at the BBB being followed by receptor-mediated translocation into the brain parenchyma (Banks 2004), and this may be exacerbated by disruption of the BBB known to follow some anesthetics and perfusion techniques (Broadwell, Balin et al. 1983). Moreover, time-course studies using i.v. insulin infusion require that systemic glycemia be maintained using glucose infusion, and this increase in glucose supply and metabolism is likely to affect brain chemistry – including, potentially, insulin levels – independent of any experimental effects (Orosco, Gerozissis et al. 1995; Gerozissis 2003; Gerozissis 2004). In addition to any transport across cerebral blood vessels, insulin acts on such vessels to modulate blood flow (as discussed above), a factor that further complicates evaluation and affects neural processes without the need for insulin transport. Finally, both direct demonstration of insulin transport across the adult BBB and molecular details of the putative transporter mechanism have remained elusive. Overall, while circulating insulin can presumably access at least the periventricular regions of the brain lacking an intact BBB, the evidence for central insulin signaling being dominated by transport of insulin from the blood does not yet justify such a conclusion.

5.3. Evidence for brain insulin production

5.3.1. Early protein studies—Some early reports of insulin-like immunoreactivity in the brain suggested that neurons are a source of insulin in the adult brain (Havrankova, Schmechel et al. 1978; Havrankova, Roth et al. 1979), supported by the report that C-peptide immunoreactivity was observed in some human pyramidal neurons (Dorn, Bernstein et al. 1982; Dorn, Rinne et al. 1982). However, the questionable specificity and high concentrations of polyclonal antibodies used in these studies limited the conclusions reachable (reviewed in (Yalow and Eng 1983)). Meanwhile, cell culture studies continued to

provide evidence of immunoreactive insulin (IRI) in neurons (Birch, Christie et al. 1984; Birch, Christie et al. 1984; Clarke, Mudd et al. 1986; Schechter, Holtzclaw et al. 1988), albeit with the caveats both of immature cells and *in vitro* conditions as well as potential issues with e.g. media composition; improved studies including insulin-free culture media confirmed these findings (Schechter, Sadiq et al. 1990). Importantly for the hypothesis that insulin might act as a neuromodulator with regulated local release, rat brain synaptosomes were shown to release IRI under depolarizing conditions (Clarke, Mudd et al. 1986), in a calcium dependent manner (Wei, Matsumoto et al. 1990) and following induction of glycolysis after glucose stimulation (Santos, Pereira et al. 1999).

5.3.2. Insulin RNA studies—If insulin is made in the brain, then an obvious requirement is for insulin mRNA to be present centrally. Presence or absence of such mRNA has proven difficult to establish definitively. Early investigations using Northern blots failed to detect proinsulin mRNA in adult rat brain (Giddings, Chirgwin et al. 1985), but *in situ* hybridization suggested the presence of preproinsulin mRNA, also in adult rat brain (Young 1986). In cell culture, Schechter and colleagues reported that 3-5% of rabbit neurons were positive for insulin mRNA, and that the same neurons had insulin immunoreactivity (Schechter, Sadiq et al. 1990; Schechter, Whitmire et al. 1994); but improved analysis *in vivo* was dependent on increased sensitivity, which arrived with the use of PCR, leading to reports of proinsulin mRNA both in embryonic rodents and then in adult rat and rabbit brain (Devaskar, Singh et al. 1993; Devaskar, Giddings et al. 1994), detailed characterization of insulin gene expression in the developing rat CNS (Schechter, Beju et al. 1996) and eventually human studies, for example in brains taken from patients with Alzheimer's disease (Rivera, Goldin et al. 2005; Steen, Terry et al. 2005). Recent work in rats has shown a dissociation between brain regions in terms of changes in insulin mRNA following a high-fat diet, suggesting that brain insulin may not simply reflect plasma insulin levels (Banas, Rouch et al. 2009).

5.3.3. Microdialysis studies—Gerozissis and colleagues have performed several elegant *in vivo* microdialysis measurements of extracellular brain insulin, showing that concentrations acutely rise with e.g. local potassium application or increased glucose levels, and importantly that the timecourse and pattern of changes in extracellular insulin is markedly distinct from that in plasma (Gerozissis, Orosco et al. 1993; Orosco, Gerozissis et al. 1995; Gerozissis, Orosco et al. 1997; Orosco, Rouch et al. 2000; Gerozissis, Rouch et al. 2001), and with dissociations again found across brain regions (Gerozissis, Rouch et al. 1998).

5.4. Summary

Some previous reviews have suggested that central insulin production may have little importance, perhaps influenced by the longstanding model of receptor-mediated transport across the BBB (e.g. (Woods, Seeley et al. 2003; Banks 2004)). However, this model has been challenged, and the body of evidence - RNA, *in vitro* and *in vivo* studies - in support of central insulin synthesis has grown to the point where, taken together, it appears convincing. A recent review concluded that “the proposal that there are two sources of insulin in the brain is consistent with the above experimental data and reconciles numerous paradoxes reported in the literature” (Gerozissis 2008), and on balance, we agree. This conclusion is obviously consistent with the main conclusion of this review, that insulin plays a critical role in modulation of cognitive processes and that impairment of such modulation leads to cognitive impairment.

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References

- Abbott MA, Wells DG, et al. The insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of CNS synapses. *Journal of Neuroscience*. 1999; 19(17):7300–8. [PubMed: 10460236]
- Aberg MA, Aberg ND, et al. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *Journal of Neuroscience*. 2000; 20(8):2896–903. [PubMed: 10751442]
- Aberg MA, Aberg ND, et al. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. *Molecular & Cellular Neurosciences*. 2003; 24(1):23–40. [PubMed: 14550766]
- Aberg ND, Johansson UE, et al. Peripheral infusion of insulin-like growth factor-I increases the number of newborn oligodendrocytes in the cerebral cortex of adult hypophysectomized rats. *Endocrinology*. 2007; 148(8):3765–72. [PubMed: 17510237]
- Ahmadian G, Ju W, et al. Tyrosine phosphorylation of GluR2 is required for insulin-stimulated AMPA receptor endocytosis and LTD. *EMBO Journal*. 2004; 23(5):1040–50. [PubMed: 14976558]
- Aimone JB, Wiles J, et al. Potential role for adult neurogenesis in the encoding of time in new memories. *Nat Neurosci*. 2006; 9(6):723–7. [PubMed: 16732202]
- Akanmu MA, Nwabudike NL, et al. Analgesic, learning and memory and anxiolytic effects of insulin in mice. *Behav Brain Res*. 2009; 196(2):237–41. [PubMed: 18840474]
- Akasaki T, Sakurai T, et al. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes intervention trial (J-EDIT). *Diabetes Metab Res Rev*. 2006; 22(5):376–84. [PubMed: 16506272]
- Anderson MF, Aberg MA, et al. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Research, Developmental Brain Research*. 2002; 134(1-2):115–22. [PubMed: 11947942]
- Annenkov A. The insulin-like growth factor (IGF) receptor type 1 (IGF1R) as an essential component of the signalling network regulating neurogenesis. *Mol Neurobiol*. 2009; 40(3):195–215. [PubMed: 19714501]
- Arsenault D, Julien C, et al. DHA Improves Cognition and Prevents Dysfunction of Entorhinal Cortex Neurons in 3xTg-AD Mice. *PLoS One*. 2011; 6(2):e17397. [PubMed: 21383850]
- Arvanitakis Z, Wilson RS, et al. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol*. 2004; 61(5):661–6. [PubMed: 15148141]
- Auestad N, Scott DT, et al. Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. *Pediatrics*. 2003; 112(3 Pt 1):e177–83. [PubMed: 12949309]
- Awad N, Gagnon M, et al. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol*. 2004; 26(8):1044–80. [PubMed: 15590460]
- Babri A, Badie H, et al. Intrahippocampal insulin improves memory in a passive-avoidance task in male wistar rats. *Brain and cognition*. 2007; 64:86–91. [PubMed: 17349729]
- Banas SM, Rouch C, et al. A dietary fat excess alters metabolic and neuroendocrine responses before the onset of metabolic diseases. *Cell Mol Neurobiol*. 2009; 29(2):157–68. [PubMed: 18773289]
- Banks WA. The source of cerebral insulin. *Eur J Pharmacol*. 2004; 490(1-3):5–12. [PubMed: 15094069]
- Banks WA. Denial versus dualism: the blood-brain barrier as an interface of the gut-brain axis. *Endocrinology*. 2006; 147(6):2609–10. [PubMed: 16707729]
- Banks WA, Jaspan JB, et al. Transport of insulin across the blood-brain barrier: saturability at euglycemic doses of insulin. *Peptides*. 1997; 18(9):1423–9. [PubMed: 9392846]
- Banks WA, Jaspan JB, et al. Effect of diabetes mellitus on the permeability of the blood-brain barrier to insulin. *Peptides*. 1997; 18(10):1577–84. [PubMed: 9437719]

- Banks WA, Jaspan JB, et al. Selective, physiological transport of insulin across the blood-brain barrier: novel demonstration by species-specific radioimmunoassays. *Peptides*. 1997; 18(8):1257–62. [PubMed: 9396070]
- Banks WA, Kastin AJ. Differential permeability of the blood-brain barrier to two pancreatic peptides: insulin and amylin. *Peptides*. 1998; 19(5):883–9. [PubMed: 9663454]
- Bateman JM, McNeill H. Insulin/IGF signalling in neurogenesis. *Cell Mol Life Sci*. 2006; 63(15): 1701–5. [PubMed: 16786222]
- Baura GD, Foster DM, et al. Saturable transport of insulin from plasma into the central nervous system of dogs in vivo. A mechanism for regulated insulin delivery to the brain. *J Clin Invest*. 1993; 92(4):1824–30. [PubMed: 8408635]
- Becker S, Wojtowicz JM. A model of hippocampal neurogenesis in memory and mood disorders. *Trends Cogn Sci*. 2007; 11(2):70–6. [PubMed: 17174137]
- Belanger A, Lavoie N, et al. Preserved LTP and water maze learning in hyperglycaemic-hyperinsulinemic ZDF rats. *Physiology & Behavior*. 2004; 83(3):483–94. [PubMed: 15581671]
- Benedict C, Hallschmid M, et al. Intranasal insulin improves memory in humans. *Psychoneuroendocrinology*. 2004; 29(10):1326–34. [PubMed: 15288712]
- Benedict C, Hallschmid M. Intranasal insulin improves memory in humans: superiority of insulin aspart. *Neuropsychopharmacology*. 2007; 32(1):239–43. [PubMed: 16936707]
- Bernstein H, Ansorge S, et al. Insulin-degrading enzyme in the AD brain: prominent localisation in neurons and senile plaques. *Neuroscience Letters*. 1999; 263:161–4. [PubMed: 10213160]
- Biessels GJ, Deary IJ, et al. Cognition and diabetes: a lifespan perspective. *Lancet Neurol*. 2008; 7(2): 184–90. [PubMed: 18207116]
- Biessels GJ, Kamal A, et al. Place learning and hippocampal synaptic plasticity in streptozotocin-induced diabetic rats. *Diabetes*. 1996; 45(9):1259–66. [PubMed: 8772732]
- Biessels GJ, Kamal A, et al. Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment. *Brain Research*. 1998; 800(1):125–35. [PubMed: 9685609]
- Bingham EM, Hopkins D, et al. The role of insulin in human brain glucose metabolism: an 18fluoro-deoxyglucose positron emission tomography study. *Diabetes*. 2002; 51(12):3384–90. [PubMed: 12453890]
- Birch NP, Christie DL, et al. Immunoreactive insulin from mouse brain cells in culture and whole rat brain. *Biochem J*. 1984; 218(1):19–27. [PubMed: 6143553]
- Birch NP, Christie DL, et al. Proinsulin-like material in mouse foetal brain cell cultures. *FEBS Lett*. 1984; 168(2):299–302. [PubMed: 6373366]
- Brands AM, Biessels GJ, et al. Cognitive functioning and brain MRI in patients with type 1 and type 2 diabetes mellitus: a comparative study. *Dement Geriatr Cogn Disord*. 2007; 23(5):343–50. [PubMed: 17374953]
- Broadwell RD, Balin BJ, et al. Brain-blood barrier?; Yes and no. *Proc Natl Acad Sci U S A*. 1983; 80(23):7352–6. [PubMed: 6580650]
- Bruehl H, Wolf OT, et al. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Res*. 2009; 1280:186–94. [PubMed: 19463794]
- Brunetti A, Fulham MJ, et al. Decreased brain glucose utilization in patients with Cushing's disease. *J Nucl Med*. 1998; 39(5):786–90. [PubMed: 9591575]
- Canal CE, Stutz SJ, et al. Glucose injections into the dorsal hippocampus or dorsolateral striatum of rats prior to T-maze training: modulation of learning rates and strategy selection. *Learn Mem*. 2005; 12(4):367–74. [PubMed: 16027177]
- Cao L, Jiao X, et al. VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat Genet*. 2004; 36(8):827–35. [PubMed: 15258583]
- Carro E, Torres-Aleman I. The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer's disease. *Eur J Pharmacol*. 2004; 490(1-3):127–33. [PubMed: 15094079]

- Chavez M, Seeley RJ, et al. Adrenalectomy increases sensitivity to central insulin. *Physiol Behav.* 1997; 62(3):631–4. [PubMed: 9272675]
- Chen DY, Stern SA, et al. A critical role for IGF-II in memory consolidation and enhancement. *Nature.* 2011; 469(7331):491–497. [PubMed: 21270887]
- Chesneau V, Perlman R, et al. Insulin-degrading enzyme does not require peroxisomal localization for insulin degradation. *Endocrinology.* 1997; 138:3444–3451. [PubMed: 9231799]
- Clarke DW, Mudd L, et al. Insulin is released from rat brain neuronal cells in culture. *J Neurochem.* 1986; 47(3):831–6. [PubMed: 3525754]
- Clegg D, Benoit S, et al. Reduced anorexi effects of insulin in obesity-prone rats fed a moderate fat diet. *American Journal of physiology.* 2005; 288:R981–986. [PubMed: 15604298]
- Cohen AD, Ziolko S, et al. P1-231: Correlation of amyloid deposition with local and distal glucose metabolism in cognitively normal elderly, MCI and Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* 2008; 4(4):T279–T280.
- Cook DG, Leverenz JB, et al. Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. *American Journal of Pathology.* 2003; 162(1):313–9. [PubMed: 12507914]
- Cornier MA, Dabelea D, et al. The metabolic syndrome. *Endocr Rev.* 2008; 29(7):777–822. [PubMed: 18971485]
- Cotero, VE.; McNay, EC. Saturated fatty acids impair, while unsaturated fatty acids enhance, hippocampal memory and metabolic processes. Society for Neuroscience annual meeting; San Diego, CA. 2010.
- Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol.* 2009; 66(3):300–5. [PubMed: 19273747]
- Craft S, Peskind E, et al. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and ApoE genotype. *Neurology.* 1998; 50:164–8. [PubMed: 9443474]
- Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *LancetNeurology.* 2004; 3(3):169–178.
- De Felice FG, Vieira MNN, et al. Protection of synapses against Alzheimer's-linked toxins: Insulin signaling prevents the pathogenic binding of A β oligomers. *Proceedings of the National Academy of Sciences.* 2009; 106(6):1971–1976.
- de la Monte SM. Insulin resistance and Alzheimer's disease. *BMB Rep.* 2009; 42(8):475–81. [PubMed: 19712582]
- de la Monte SM, Tong M, et al. Ceramide-Mediated Insulin Resistance and Impairment of Cognitive-Motor Functions. *Journal of Alzheimer's Disease.* 2010; 21(3):967–984.
- de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling and malfunction in the central nervous system: relevance to Alzheimer's disease. *J Alzheimers Dis.* 2005; 7(1):45–61. [PubMed: 15750214]
- de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. *J Diabetes Sci Technol.* 2008; 2(6):1101–13. [PubMed: 19885299]
- de Quervain DJ, Roozendaal B, et al. Stress and glucocorticoids impair retrieval of long-term spatial memory. *Nature.* 1998; 394(6695):787–90. [PubMed: 9723618]
- Degroot A, Kornecook T, et al. Glucose increases hippocampal extracellular acetylcholine levels upon activation of septal GABA receptors. *Brain Research.* 2003; 979(1-2):71–77. [PubMed: 12850573]
- Dempsey RJ, Sailor KA, et al. Stroke-induced progenitor cell proliferation in adult spontaneously hypertensive rat brain: effect of exogenous IGF-1 and GDNF. *Journal of Neurochemistry.* 2003; 87(3):586–97. [PubMed: 14535942]
- Deng W, Aimone JB, et al. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci.* 2010; 11(5):339–50. [PubMed: 20354534]
- Devaskar SU, Giddings SJ, et al. Insulin gene expression and insulin synthesis in mammalian neuronal cells. *J Biol Chem.* 1994; 269(11):8445–54. [PubMed: 8132571]

- Devaskar SU, Singh BS, et al. Insulin II gene expression in rat central nervous system. *Regul Pept.* 1993; 48(1-2):55–63. [PubMed: 8265817]
- Dhikav V, Anand KS. Glucocorticoids may initiate Alzheimer's disease: a potential therapeutic role for mifepristone (RU-486). *Medical Hypotheses.* 2007; 68(5):1088–92. [PubMed: 17107752]
- Ding Q, Vaynman S, et al. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience.* 2006; 140(3):823–33. [PubMed: 16650607]
- Dorn A, Bernstein HG, et al. Insulin-like immunoreactivity in the human brain- A preliminary report. *Histochemistry.* 1982; 74(2):293–300. [PubMed: 6757198]
- Dorn A, Rinne A, et al. C-peptide immunoreactive neurons in human brain. *Acta Histochemica.* 1982; 70(2):326–30. [PubMed: 6810639]
- Drapeau E, Mayo W, et al. Spatial memory performances of aged rats in the water maze predict levels of hippocampal neurogenesis. *Proc Natl Acad Sci U S A.* 2003; 100(24):14385–90. [PubMed: 14614143]
- Duffy KR, Pardridge WM. Blood-brain barrier transcytosis of insulin in developing rabbits. *Brain Res.* 1987; 420(1):32–8. [PubMed: 3315116]
- Dupret D, Revest JM, et al. Spatial reational memory requires hippocampal adult neurogenesis. *PLoS One.* 2008; 3(4):e1959. [PubMed: 18509506]
- Eng J, Yalow RS. Evidence against extrapancreatic insulin synthesis. *Proc Natl Acad Sci U S A.* 1981; 78(7):4576–8. [PubMed: 6270683]
- Erickson EJ, Watts KD, et al. Septal co-infusions of glucose with a GABAB agonist impair memory. *Neurobiol Learn Mem.* 2006; 85(1):66–70. [PubMed: 16226043]
- Ernst C, Olson AK, et al. Antidepressant effects of exercise: evidence for an adult-neurogenesis hypothesis? *J Psychiatry Neurosci.* 2006; 31(2):84–92. [PubMed: 16575423]
- Farr SA, Yamada KA, et al. Obesity and Hypertriglyceridemia Produce Cognitive Impairment. *Endocrinology.* 2008; 149(5):2628–2636. [PubMed: 18276751]
- Farris W, Mansourian S, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *PNAS.* 2003; 100(7):4162–7. [PubMed: 12634421]
- Fontan-Lozano A, Lopez-Lluch G, et al. Molecular bases of caloric restriction regulation of neuronal synaptic plasticity. *Mol Neurobiol.* 2008; 38(2):167–77. [PubMed: 18759009]
- Frank HJ, Jankovic-Vokes T, et al. Enhanced insulin binding to blood-brain barrier in vivo and to brain microvessels in vitro in newborn rabbits. *Diabetes.* 1985; 34(8):728–33. [PubMed: 3894116]
- Frolich L, Blum-Degen D, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *Journal of Neural transmission.* 1998; 105:423–438. [PubMed: 9720972]
- Gasparini L, Gouras GK, et al. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. *Journal of Neuroscience.* 2001; 21(8):2561–70. [PubMed: 11306609]
- Gasparini L, Netzer W, et al. Does insulin dysfunction play a role in Alzheimer's disease? *Trends in Pharmacological Sciences.* 2002; 23:288–293. [PubMed: 12084635]
- Gerges NZ, Aleisa AM, et al. Impaired long-term potentiation in obese Zucker rats: possible involvement of presynaptic mechanism. *Neuroscience.* 2003; 120(2):535–9. [PubMed: 12890522]
- Gerozissis K. Brain insulin: regulation, mechanisms of action and functions. *Cellular and Molecular Neurobiology.* 2003; 23(1):1–25. [PubMed: 12701881]
- Gerozissis K. Brain insulin and feeding: a bi-directional communication. *Eur J Pharmacol.* 2004; 490(1-3):59–70. [PubMed: 15094073]
- Gerozissis K. Brain insulin, energy and glucose homeostasis; genes, environment and metabolic pathologies. *Eur J Pharmacol.* 2008; 585(1):38–49. [PubMed: 18407262]
- Gerozissis K. Diabetes, insulin and Alzheimer's Disease. Springer; Berlin Heidelberg; 2010. The Brain-insulin Connection, Metabolic Diseases and Related Pathologies; p. 21–42.
- Gerozissis K. The Brain-insulin Connection, Metabolic Diseases and Related Pathologies. Research and Perspectives in Alzheimer's Disease. 2010

- Gerozissis K, Orosco M, et al. Basal and hyperinsulinemia-induced immunoreactive hypothalamic insulin changes in lean and genetically obese Zucker rats revealed by microdialysis. *Brain Res.* 1993; 611(2):258–63. [PubMed: 8334519]
- Gerozissis K, Orosco M, et al. Insulin responses to a fat meal in hypothalamic microdialysates and plasma. *Physiol Behav.* 1997; 62(4):767–72. [PubMed: 9284495]
- Gerozissis K, Rouch C, et al. A potential role of central insulin in learning and memory related to feeding. *Cell Mol Neurobiol.* 2001; 21(4):389–401. [PubMed: 11775068]
- Gerozissis K, Rouch C, et al. Brain insulin response to feeding in the rat is both macronutrient and area specific. *Physiol Behav.* 1998; 65(2):271–5. [PubMed: 9855476]
- Giddings SJ, Chirgwin J, et al. Evaluation of rat insulin messenger RNA in pancreatic and extrapancreatic tissues. *Diabetologia.* 1985; 28(6):343–7. [PubMed: 2412922]
- Gip P, Hagiwara G, et al. Glucocorticoids influence brain glycogen levels during sleep deprivation. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology.* 2004; 286(6):R1057–R1062.
- Gispen W, Biessels G. Cognition and synaptic plasticity in diabetes mellitus. *Trends in Neuroscience.* 2000; (23):542–549.
- Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci.* 2000; 23(11):542–9. [PubMed: 11074263]
- Giuffrida ML, Caraci F, et al. Beta-amyloid monomers are neuroprotective. *J Neurosci.* 2009; 29(34):10582–7. [PubMed: 19710311]
- Gold P. Role of glucose in regulating the brain and cognition. *American Journal of Clinical Nutrition.* 1995; 61:987S–995S. [PubMed: 7900698]
- Gold P. Glucose and age-related changes in memory. *Neurobiology of Aging.* 2005; 26S:S60–64.
- Gold PE. Role of glucose in regulating the brain and cognition. *Am J Clin Nutr.* 1995; 61(4 Suppl):987S–995S. [PubMed: 7900698]
- Goodner CJ, Berrie MA. The failure of rat hypothalamic tissues to take up labeled insulin in vivo or to respond to insulin in vitro. *Endocrinology.* 1977; 101(2):605–12. [PubMed: 885120]
- Gould E, Beylin A, et al. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci.* 1999; 2(3):260–5. [PubMed: 10195219]
- Gould E, Woolley CS, et al. The hippocampal formation: morphological changes induced by thyroid, gonadal and adrenal hormones. *Psychoneuroendocrinology.* 1991; 16(1-3):67–84. [PubMed: 1961845]
- Greenwood C, Winocur G. Learning and memory impairment in rats fed a high saturated fat diet. *behavioral & Neural Biology.* 1990; 53:74–87. [PubMed: 2302144]
- Greenwood CE, Winocur G. Glucose treatment reduces memory deficits in young adult rats fed high-fat diets. *Neurobiology of Learning & Memory.* 2001; 75(2):179–89. [PubMed: 11222059]
- Greenwood CE, Winocur G. High-fat diets, insulin resistance and declining cognitive function. *Neurobiol Aging.* 2005; 26 1:42–5. [PubMed: 16257476]
- Grillo CA, Piroli GG, et al. Insulin-stimulated translocation of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. *Brain Res.* 2009; 1296:35–45. [PubMed: 19679110]
- Group, D. C. a. C. R. The effect of intensive treatment of diabetes on the development and progression of long-term complications in diabetes mellitus. *New England Journal of Medicine.* 1993; 329:977–986. [PubMed: 8366922]
- Group, U. P. D. S. UKPDS. *Diabetologia.* 1991; 34(12):877–90. [PubMed: 1778353]
- Haj-ali V, Mohaddes G, et al. Intracerebroventricular insulin improves spatial learning and memory in male Wistar rats. *Behav Neurosci.* 2009; 123(6):1309–14. [PubMed: 20001114]
- Hamilton-Wessler M, Ader M, et al. Mode of transcapillary transport of insulin and insulin analog NN304 in dog hindlimb: evidence for passive diffusion. *Diabetes.* 2002; 51(3):574–82. [PubMed: 11872653]
- Hasselbalch SG, Knudsen GM, et al. No effect of insulin on glucose blood-brain barrier transport and cerebral metabolism in humans. *Diabetes.* 1999; 48(10):1915–21. [PubMed: 10512354]

- Havrankova J, Roth J, et al. Concentrations of insulin and insulin receptors in the brain are independent of peripheral insulin levels. Studies of obese and streptozotocin-treated rodents. *J Clin Invest.* 1979; 64(2):636–42. [PubMed: 156737]
- Havrankova J, Schmechel D, et al. Identification of insulin in rat brain. *Proc Natl Acad Sci U S A.* 1978; 75(11):5737–41. [PubMed: 364489]
- Henneberg N, Hoyer S. Short-term or long-term intracerebroventricular (i.c.v.) infusion of insulin exhibits a discrete anabolic effect on cerebral energy metabolism in the rat. *Neuroscience Letters.* 1994; 175(1-2):153–6. [PubMed: 7970199]
- Ho L, Qin W, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB Journal.* 2004; 18:902–904. [PubMed: 15033922]
- Hoyer S, Henneberg N, et al. Brain glucose metabolism is controlled by amplification and desensitization of the neuronal insulin receptor. *Annals of the New York Academy of Sciences.* 1996; 777:374–9. [PubMed: 8624116]
- Hoyer S, Muller D, et al. Desensitization of brain insulin receptor. Effect on glucose/energy and related metabolism. *Journal of Neural Transmission Supplementum.* 1994; 44:259–68. [PubMed: 7897397]
- Huang CC, Lee CC, et al. An investigation into signal transduction mechanisms involved in insulin-induced long-term depression in the CA1 region of the hippocampus. *Journal of Neurochemistry.* 2004; 89(1):217–31. [PubMed: 15030406]
- Issa AM, Mojica WA, et al. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. *Dement Geriatr Cogn Disord.* 2006; 21(2):88–96. [PubMed: 16340205]
- Izumi Y, Yamada KA, et al. Effects of insulin on long-term potentiation in hippocampal slices from diabetic rats. *Diabetologia.* 2003; 46(7):1007–12. [PubMed: 12827244]
- Jacobson AM, Musen G, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med.* 2007; 356(18):1842–52. [PubMed: 17476010]
- Janson J, Laedtke T, et al. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes.* 2004; 53(2):474–81. [PubMed: 14747300]
- Julien C, Tremblay C, et al. High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. *Neurobiol Aging.* 31(9):1516–31. [PubMed: 18926603]
- Kamal A, Biessels GJ, et al. Learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: interaction of diabetes and ageing. *Diabetologia.* 2000; 43(4):500–6. [PubMed: 10819245]
- King GL, Johnson SM. Receptor-mediated transport of insulin across endothelial cells. *Science.* 1985; 227(4694):1583–6. [PubMed: 3883490]
- Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev.* 2008; 29(4):494–511. [PubMed: 18436709]
- Korol DL, Gold PE. Glucose, memory, and aging. *American Journal of Clinical Nutrition.* 1998; 67(4):764S–771S.
- Lafenêtre, P.; Leske, O., et al. Exercise can rescue recognition memory impairment in a model with reduced adult hippocampal neurogenesis. 2009.
- Lang BT, Yan Y, et al. Impaired neurogenesis in adult type-2 diabetic rats. *Brain Res.* 2009; 1258:25–33. [PubMed: 19138677]
- Laron Z. Insulin and the brain. *Arch Physiol Biochem.* 2009; 115(2):112–6. [PubMed: 19485707]
- Lee CC, Kuo YM, et al. Insulin rescues amyloid β -induced impairment of hippocampal long-term potentiation. *Neurobiology of Aging.* 2009; 30(3):377–387. [PubMed: 17692997]
- Leibson C, Rocca W, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. *American Journal of Epidemiology.* 1997; 145:301–308. [PubMed: 9054233]
- Levin BE, Triscari J, et al. Abnormal sympatho-adrenal function and plasma catecholamines in obese Zucker rats. *Pharmacol Biochem Behav.* 1980; 13(1):107–13. [PubMed: 7403213]
- Liao FF, Xu H. Insulin Signaling in Sporadic Alzheimer's Disease. *Sci Signal.* 2009; 2(74):pe36. [PubMed: 19509405]
- Lin JW, Ju W, et al. Distinct molecular mechanisms and divergent endocytotic pathways of AMPA receptor internalization. *Nature Neuroscience.* 2000; 3(12):1282–90.

- Lindqvist A, Mohapel P, et al. High-fat diet impairs hippocampal neurogenesis in male rats. *Eur J Neurol*. 2006; 13(12):1385–8. [PubMed: 17116226]
- Luchsinger JA, Tang MX, et al. Diabetes Mellitus and Risk of Alzheimer's Disease and Dementia with Stroke in a Multiethnic Cohort. *Am J Epidemiol*. 2001; 154(7):635–641. [PubMed: 11581097]
- Lupien SJ, McEwen BS, et al. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*. 2009; 10(6):434–45. [PubMed: 19401723]
- MacLean CH, Newberry SJ, et al. Effects of omega-3 fatty acids on cancer risk: a systematic review. *JAMA*. 2006; 295(4):403–15. [PubMed: 16434631]
- Malberg JE, Eisch AJ, et al. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci*. 2000; 20(24):9104–10. [PubMed: 11124987]
- Man HY, Lin JW, et al. Regulation of AMPA receptor-mediated synaptic transmission by clathrin-dependent receptor internalization. *Neuron*. 2000; 25(3):649–62. erratum appears in *Neuron* 2001 Jan;29(1):307. [PubMed: 10774732]
- Margolis RU, Altszuler N. Insulin in the cerebrospinal fluid. *Nature*. 1967; 215(5108):1375–6. [PubMed: 6055448]
- McEwen BS, Magarinos AM, et al. Studies of hormone action in the hippocampal formation: possible relevance to depression and diabetes. *Journal of Psychosomatic Research*. 2002; 53(4):883–90. [PubMed: 12377298]
- McGaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. *Current Opinion in Neurobiology*. 2002; 12(2):205–10. [PubMed: 12015238]
- McNay E. The impact of recurrent hypoglycemia on cognitive function in aging. *Neurobiology of Aging*. 2005; 26:S76–79.
- McNay E, Cotero V. Mini-review: impact of recurrent hypoglycemia on cognitive and brain function. *Physiology and Behavior*. 2010; 100(3):234–8. [PubMed: 20096711]
- McNay E, Gold P. Extracellular glucose concentrations in the rat hippocampus measured by zero-net-flux: effects of microdialysis flow rate, strain, and age. *J Neurochem*. 1999; 72:785–790. [PubMed: 9930754]
- McNay E, Ong C, et al. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. *Neurobiology of Learning and Memory*. 2010; 93(4):546–53. [PubMed: 20176121]
- McNay EC, Canal CE, et al. Modulation of memory with septal injections of morphine and glucose: effects on extracellular glucose levels in the hippocampus. *Physiol Behav*. 2006; 87(2):298–303. [PubMed: 16343563]
- McNay EC, Fries TM, et al. Decreases in rat extracellular hippocampal glucose concentration associated with cognitive demand during a spatial task. *Proceedings of the National Academy of Sciences of the United States of America*. 2000; 97(6):2881–5. [PubMed: 10706633]
- McNay EC, Gold PE. Memory modulation across neural systems: intra-amygdala glucose reverses deficits caused by intraseptal morphine on a spatial task but not on an aversive task. *Journal of Neuroscience*. 1998; 18(10):3853–8. [PubMed: 9570814]
- McNay EC, Gold PE. Age-related differences in hippocampal extracellular fluid glucose concentration during behavioral testing and following systemic glucose administration. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*. 2001; 56(2):B66–71.
- McNay EC, Gold PE. Food for thought: fluctuations in brain extracellular glucose provide insight into the mechanisms of memory modulation. *Cognitive and Behavioural Neuroscience Reviews*. 2002; 1:264–280.
- McNay, EC.; Green, PK., et al. Recurrent hypoglycemia and central insulin resistance: diverse mechanisms producing hippocampal amyloid accumulation. ICAD annual meeting; Honolulu, HI. 2010.
- McNay EC, Ong CT, et al. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. *Neurobiol Learn Mem*. 2010
- McNay EC, Sherwin RS. Effect of recurrent hypoglycemia on spatial cognition and cognitive metabolism in normal and diabetic rats. *Diabetes*. 2004; 53(2):418–25. [PubMed: 14747293]
- McNay EC, Williamson A, et al. Cognitive and neural hippocampal effects of long-term moderate recurrent hypoglycemia. *Diabetes*. 2006; 55(4):1088–95. [PubMed: 16567533]

- Messier C, Awad N, et al. The relationships between atherosclerosis, heart disease, type 2 diabetes and dementia. *Neurol Res.* 2004; 26(5):567–72. [PubMed: 15265276]
- Mielke J, Taghibiglou C, et al. A biochemical and functional characterization of diet-induced brain insulin resistance. *Journal of Neurochemistry.* 2005; 93:1568–1578. [PubMed: 15935073]
- Moosavi M, Naghdi N, et al. Intra CA1 insulin microinjection improves memory consolidation and retrieval. *Peptides.* 2007; 28(5):1029–34. [PubMed: 17360072]
- Moosavi M, Naghdi N, et al. The effect of intrahippocampal insulin microinjection on spatial learning and memory. *Hormones and Behavior.* 2006; 50:748–752. [PubMed: 16890939]
- Moosavi M, Naghdi N, et al. Insulin protects against stress-induced impairments in water maze performance. *Behavioural Brain Research.* 2007; 176(2):230–6. [PubMed: 17116337]
- Morelli L, Llovera RE, et al. Insulin-degrading enzyme in brain microvessels: proteolysis of amyloid {beta} vasculotropic variants and reduced activity in cerebral amyloid angiopathy. *J Biol Chem.* 2004; 279(53):56004–13. [PubMed: 15489232]
- Moroz N, Tong M, et al. Limited Alzheimer-type neurodegeneration in experimental obesity and type 2 diabetes mellitus. *J Alzheimers Dis.* 2008; 15(1):29–44. [PubMed: 18780965]
- Morris MC, Evans DA, et al. Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol.* 2003; 60(2):194–200. [PubMed: 12580703]
- Neumann KF, Rojo L, et al. Insulin resistance and Alzheimer's disease: molecular links & clinical implications. *Curr Alzheimer Res.* 2008; 5(5):438–47. [PubMed: 18855585]
- O'Malley D, Harvey J. MAPK-dependent actin cytoskeletal reorganization underlies BK channel activation by insulin. *European Journal of Neuroscience.* 2007; 25(3):673–82. [PubMed: 17298596]
- Ono T, Steffens AB, et al. Influence of peripheral and intracerebroventricular glucose and insulin infusions on peripheral and cerebrospinal fluid glucose and insulin levels. *Physiol Behav.* 1983; 30(2):301–6. [PubMed: 6342012]
- Oomura Y, Nakamura T, et al. Effect of free fatty acid on the rat lateral hypothalamic neurons. *Physiol Behav.* 1975; 14(04):483–6. [PubMed: 1135293]
- Orosco M, Gerozissis K, et al. Feeding-related immunoreactive insulin changes in the PVN-VMH revealed by microdialysis. *Brain Research.* 1995; 671:149–58. [PubMed: 7728527]
- Orosco M, Rouch C, et al. Activation of hypothalamic insulin by serotonin is the primary event of the insulin-serotonin interaction involved in the control of feeding. *Brain Res.* 2000; 872(1-2):64–70. [PubMed: 10924676]
- Ott A, Stolk RP, et al. Diabetes mellitus and the risk of dementia. *Neurology.* 1999; 53(9):1937. [PubMed: 10599761]
- Pardridge WM. Receptor-mediated peptide transport through the blood-brain barrier. *Endocr Rev.* 1986; 7(3):314–30. [PubMed: 3017689]
- Pardridge WM, Eisenberg J, et al. Human blood-brain barrier insulin receptor. *J Neurochem.* 1985; 44(6):1771–8. [PubMed: 2859355]
- Park CR, Seeley RJ, et al. Intracerebroventricular insulin enhances memory in a passive avoidance task. *Physiology and Behaviour.* 2000; 68(4):509–514.
- Parsons MW, Gold PE. Glucose enhancement of memory in elderly humans: an inverted-U dose-response curve. *Neurobiology of Aging.* 1992; 13(3):401–4. [PubMed: 1625769]
- Pedersen WA, McMillan PJ, et al. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. *Exp Neurol.* 2006; 199(2):265–73. [PubMed: 16515786]
- Pirola GG, Grillo CA, et al. Peripheral glucose administration stimulates the translocation of GLUT8 glucose transporter to the endoplasmic reticulum in the rat hippocampus. *Journal of Comparative Neurology.* 2002; 452(2):103–14. [PubMed: 12271485]
- Pirola GG, Grillo CA, et al. Corticosterone impairs insulin-stimulated translocation of GLUT4 in the rat hippocampus. *Neuroendocrinology.* 2007; 85(2):71–80. [PubMed: 17426391]
- Plata-Salaman CR. Insulin in the cerebrospinal fluid. *Neurosci Biobehav Rev.* 1991; 15(2):243–58. [PubMed: 1852315]
- Pocai A, Lam T, et al. Hypothalamic K(ATP) channels control hepatic glucose production. *Nature.* 2005; 434:1026–1031. [PubMed: 15846348]

- Quirarte GL, Roozendaal B, et al. Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America*. 1997; 94(25):14048–53. [PubMed: 9391150]
- Ramakrishnan R, Namasivayam A. Norepinephrine and epinephrine levels in the brain of alloxan diabetic rats. *Neuroscience Letters*. 1995; 186(2-3):200–202. [PubMed: 7777196]
- Ramirez-Amaya V, Marrone DF, et al. Integration of new neurons into functional neural networks. *J Neurosci*. 2006; 26(47):12237–41. [PubMed: 17122048]
- Reagan L. Neuronal Insulin signal transduction mechanisms in diabetes phenotypes. *Neurobiology of Aging*. 2005; 26S:S56–59.
- Reagan LP. Diabetes as a chronic metabolic stressor: Causes, consequences and clinical complications. *Experimental Neurology*. 2011 In Press, Corrected Proof.
- Reger M, Watson G, et al. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiology of Aging*. 2006; 27:451–458. [PubMed: 15964100]
- Reger MA, Watson GS, et al. Effects of intranasal insulin on cognition in memory-impaired older adults: Modulation by APOE genotype. *Neurobiology of Aging*. 2006; 27(3):451–458. [PubMed: 15964100]
- Reger MA, Watson GS, et al. Intranasal insulin administration dose- dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. *J Alzheimers Dis*. 2008; 13(3):323–31. [PubMed: 18430999]
- Reger MA, Watson GS, et al. Intranasal insulin improves cognition and modulates {beta}-amyloid in early AD. *Neurology*. 2008; 70(6):440–448. [PubMed: 17942819]
- Reiser M, Lenz E, et al. Insulin-like immunoreactivity in human cerebrospinal-fluid is independent of insulin blood levels. *Hum Neurobiol*. 1985; 4(1):53–5. [PubMed: 3888934]
- Rivera EJ, Goldin A, et al. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis*. 2005; 8(3):247–68. [PubMed: 16340083]
- Roozendaal B. Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiology of Learning & Memory*. 2002; 78(3):578–95. [PubMed: 12559837]
- Roozendaal B, McEwen BS, et al. Stress, memory and the amygdala. *Nat Rev Neurosci*. 2009; 10(6):423–33. [PubMed: 19469026]
- Ross AP, Bartness TJ, et al. A high fructose diet impairs spatial memory in male rats. *Neurobiology of Learning and Memory*. 2009; 92(3):410–416. [PubMed: 19500683]
- Santos MS, Pereira EM, et al. Stimulation of immunoreactive insulin release by glucose in rat brain synaptosomes. *Neurochem Res*. 1999; 24(1):33–6. [PubMed: 9973234]
- Sapolsky RM. Glucocorticoid toxicity in the hippocampus: reversal by supplementation with brain fuels. *J Neurosci*. 1986; 6(8):2240–4. [PubMed: 3746406]
- Schechter R, Beju D, et al. Preproinsulin I and II mRNAs and insulin electron microscopic immunoreaction are present within the rat fetal nervous system. *Brain Res*. 1996; 736(1-2):16–27. [PubMed: 8930304]
- Schechter R, Holtzclaw L, et al. Insulin synthesis by isolated rabbit neurons. *Endocrinology*. 1988; 123(1):505–13. [PubMed: 3289897]
- Schechter R, Sadiq HF, et al. Insulin and insulin mRNA are detected in neuronal cell cultures maintained in an insulin-free/serum-free medium. *J Histochem Cytochem*. 1990; 38(6):829–36. [PubMed: 2186089]
- Schechter R, Whitmire J, et al. Immunohistochemical and in situ hybridization study of an insulin-like substance in fetal neuron cell cultures. *Brain Res*. 1994; 636(1):9–27. [PubMed: 8156415]
- Schubert M, Gautam D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. *PNAS*. 2004; 101:3100–3105. [PubMed: 14981233]
- Schubert M, Gautam D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci U S A*. 2004; 101(9):3100–5. [PubMed: 14981233]

- Schwartz MW, Bergman RN, et al. Evidence for entry of plasma insulin into cerebrospinal fluid through an intermediate compartment in dogs. Quantitative aspects and implications for transport. *J Clin Invest.* 1991; 88(4):1272–81. [PubMed: 1918377]
- Schwartz MW, Sipols A, et al. Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. *Am J Physiol.* 1990; 259(3 Pt 1):E378–83. [PubMed: 2205107]
- Sequist E, Damberg G, et al. The effect of insulin on in vivo cerebral glucose concentrations and rates of glucose transport/metabolism in humans. *Diabetes.* 2001; 50(2203-2209)
- Shah AA, Parent MB. Septal infusions of glucose or pyruvate, but not fructose, produce avoidance deficits when co-infused with the GABA agonist muscimol. *Neurobiology of Learning & Memory.* 2003; 79(3):243–251. [PubMed: 12676523]
- Skeberdis VA, Lan Jy, et al. Insulin promotes rapid delivery of N-methyl-d- aspartate receptors to the cell surface by exocytosis. *Proceedings of the National Academy of Sciences.* 2001; 98(6):3561–3566.
- Spanwick D, Smith MA, et al. Insulin activates ATP-sensitive K⁺ channels in hypothalamic neurons of lean, but not obese, rats. *Nature Neuroscience.* 2000; 3(8):757–758.
- Stangl D, Thuret S. Impact of diet on adult hippocampal neurogenesis. *Genes Nutr.* 2009; 4(4):271–82. [PubMed: 19685256]
- Steen E, Terry B, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease: is this type 3 diabetes? *Journal of Alzheimer's Disease.* 2005; 7:63–80.
- Stefani MR, Gold PE. Intrahippocampal infusions of k-atp channel modulators influence spontaneous alternation performance: relationships to acetylcholine release in the hippocampus. *Journal of Neuroscience.* 2001; 21(2):609–614. [PubMed: 11160440]
- Steffens AB, Scheurink AJ, et al. Penetration of peripheral glucose and insulin into cerebrospinal fluid in rats. *Am J Physiol.* 1988; 255(2 Pt 2):R200–4. [PubMed: 3044143]
- Steil GM, Ader M, et al. Transendothelial insulin transport is not saturable in vivo. No evidence for a receptor-mediated process. *J Clin Invest.* 1996; 97(6):1497–503. [PubMed: 8617883]
- Stranahan AM, Arumugam TV, et al. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nat Neurosci.* 2008; 11(3):309–17. [PubMed: 18278039]
- Stranahan AM, Arumugam TV, et al. Mineralocorticoid receptor activation restores medial perforant path LTP in diabetic rats. *Synapse.* 2010; 64(7):528–32. [PubMed: 20196138]
- Stranahan AM, Lee K, et al. Hippocampal gene expression patterns underlying the enhancement of memory by running in aged mice. *Neurobiol Aging.* 2010; 31(11):1937–49. [PubMed: 19070401]
- Stranahan AM, Lee K, et al. Accelerated cognitive aging in diabetic rats is prevented by lowering corticosterone levels. *Neurobiol Learn Mem.* 2008; 90(2):479–83. [PubMed: 18579418]
- Stranahan AM, Mattson MP. Bidirectional metabolic regulation of neurocognitive function. *Neurobiol Learn Mem.* 2011
- Sun MK, Alkon DL. Links between Alzheimer's disease and diabetes. *Drugs Today (Barc).* 2006; 42(7):481–9. [PubMed: 16894402]
- Townsend M, Mehta T, et al. Soluble A β Inhibits Specific Signal Transduction Cascades Common to the Insulin Receptor Pathway. *Journal of Biological Chemistry.* 2007; 282(46):33305–33312. [PubMed: 17855343]
- Triguero D, Buciak J, et al. Capillary depletion method for quantification of blood-brain barrier transport of circulating peptides and plasma proteins. *J Neurochem.* 1990; 54(6):1882–8. [PubMed: 2338547]
- Unger J, McNeill TH, et al. Distribution of insulin receptor-like immunoreactivity in the rat forebrain. *Neuroscience.* 1989; 31(1):143–57. [PubMed: 2771055]
- Unger JW, Moss AM, et al. Immunohistochemical localization of insulin receptors and phosphotyrosine in the brainstem of the adult rat. *Neuroscience.* 1991; 42(3):853–61. [PubMed: 1720228]

- van den Berg E, Kloppenborg RP, et al. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim Biophys Acta*. 2009; 1792(5):470–81. [PubMed: 18848880]
- van den Berg E, Reijmer YD, et al. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. *Diabetologia*. 2010; 53(1):58–65. [PubMed: 19882137]
- van der Borgh K, Kohnke R, et al. Reduced neurogenesis in the rat hippocampus following high fructose consumption. *Regul Pept*. 2011; 167(1):26–30. [PubMed: 21115071]
- van der Heide LP, Kamal A, et al. Insulin modulates hippocampal activity-dependent synaptic plasticity in a N-methyl-D-aspartate receptor and phosphatidylinositol-3-kinase-dependent manner. *Journal of Neurochemistry*. 2005; 94(4):1158–66. [PubMed: 16092951]
- Vannucci S, Koehler-Stec E, et al. GluT4 glucose transporter expression in rodent brain: effect of diabetes. *Brain Research*. 1998; 797:1–11. [PubMed: 9630471]
- Vetiska SM, Ahmadian G, et al. GABAA receptor-associated phosphoinositide 3-kinase is required for insulin-induced recruitment of postsynaptic GABAA receptors. *Neuropharmacology*. 2007; 52(1):146–55. [PubMed: 16890252]
- Wallum BJ, Taborsky GJ Jr, et al. Cerebrospinal fluid insulin levels increase during intravenous insulin infusions in man. *J Clin Endocrinol Metab*. 1987; 64(1):190–4. [PubMed: 3536982]
- Wang R, Cruciani-Guglielmacci C, et al. Effects of oleic acid on distinct populations of neurons in the hypothalamic arcuate nucleus are dependent on extracellular glucose levels. *J Neurophysiol*. 2006; 95(3):1491–8. [PubMed: 16306178]
- Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS Drugs*. 2003; 17(1):27–45. [PubMed: 12467491]
- Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. *European Journal of Pharmacology*. 2004; 490(1-3):97–113. [PubMed: 15094077]
- Wei LT, Matsumoto H, et al. Release of immunoreactive insulin from rat brain synaptosomes under depolarizing conditions. *J Neurochem*. 1990; 54(5):1661–5. [PubMed: 2182775]
- Wei Qiao Q, Marshal FF. Insulin, insulin-degrading enzyme and amyloid- β peptide in Alzheimer's disease: review and hypothesis. *Neurobiology of Aging*. 2006; 27(2):190–198. [PubMed: 16399206]
- Williams CL, McGaugh JL. Reversible lesions of the nucleus of the solitary tract attenuate the memory-modulating effects of posttraining epinephrine. *Behavioral Neuroscience*. 1993; 107(6):955–62. [PubMed: 8136070]
- Winocur G, Greenwood CE. Studies of the effects of high fat diets on cognitive function in a rat model. *Neurobiol Aging*. 2005; 26 1:46–9. [PubMed: 16219391]
- Winocur G, Greenwood CE, et al. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. *Behav Neurosci*. 2005; 119(5):1389–95. [PubMed: 16300445]
- Winocur G, Greenwood CE, et al. Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. *Behavioral Neuroscience*. 2005; 119(5):1389–95. [PubMed: 16300445]
- Woods SC, Porte D Jr. Relationship between plasma and cerebrospinal fluid insulin levels of dogs. *Am J Physiol*. 1977; 233(4):E331–4. [PubMed: 910946]
- Woods SC, Seeley RJ, et al. Insulin and the blood-brain barrier. *Curr Pharm Des*. 2003; 9(10):795–800. [PubMed: 12678878]
- Wozniak M, Rydzewski B, et al. The cellular and physiological actions of insulin in the central nervous system. *Neurochem Int*. 1993; 22(1):1–10. [PubMed: 8443563]
- Wrighten SA, Piroli GG, et al. A look inside the diabetic brain: Contributors to diabetes-induced brain aging. *Biochim Biophys Acta*. 2009; 1792(5):444–53. [PubMed: 19022375]
- Yalow RS, Eng J. Insulin in the central nervous system. *Adv Metab Disord*. 1983; 10:341–54. [PubMed: 6364718]
- Young WS 3rd. Periventricular hypothalamic cells in the rat brain contain insulin mRNA. *Neuropeptides*. 1986; 8(2):93–7. [PubMed: 3531909]

- Zhao L, Teter B, et al. Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: implications for Alzheimer's disease intervention. *Journal of Neuroscience*. 2004; 24(49):11120–6. [PubMed: 15590928]
- Zhao W, Chen H, et al. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J Biol Chem*. 1999; 274(49):34893–902. [PubMed: 10574963]
- Zhao WQ, Chen H, et al. Insulin and the insulin receptor in experimental models of learning and memory. *European Journal of Pharmacology*. 2004; 490:71–81. [PubMed: 15094074]
- Zhao WQ, De Felice FG, et al. Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J*. 2008; 22(1):246–260. [PubMed: 17720802]
- Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. *Mol Cell Endocrinol*. 2001; 177(1-2):125–34. [PubMed: 11377828]
- Zhao WQ, Lacor PN, et al. Insulin receptor dysfunction impairs cellular clearance of neurotoxic oligomeric α {beta}. *J Biol Chem*. 2009; 284(28):18742–53. [PubMed: 19406747]
- Zhao WQ, Townsend M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. *Biochim Biophys Acta*. 2009; 1792(5):482–96. [PubMed: 19026743]

- Insulin is a key component of hippocampal memory processing.
- Insulin resistance occurs centrally and produces cognitive impairment.
- Specific molecular mechanisms for insulin's role are identified.
- Evidence for central synthesis of insulin is now substantial.