Published in final edited form as:

Curr Opin Pharmacol. 2007 December ; 7(6): 633–637.

INSULIN SIGNALING EFFECTS ON MEMORY AND MOOD

Lawrence P. Reagan

Department of Pharmacology, Physiology and Neuroscience, University of South Carolina School of Medicine, Columbia, SC 29208 USA

Abstract

The escalating obesity/diabetes epidemic is an important health care issue that has critical socio-economic ramifications. The complications of diabetes/obesity phenotypes extend to the central nervous system, including the hippocampus, a brain region that is particularly vulnerable to hyperglycemia and insulin resistance. Deficits in hippocampal synaptic plasticity observed in diabetes ultimately have deleterious consequences upon cognitive function. For example, recent studies using brain imaging technologies have identified cerebral atrophy in diabetic patients, suggesting that the neuroanatomical changes observed in experimental models of diabetes may accurately reflect what is occurring in the clinical setting. Deficits in insulin receptor signaling and impairments in hypothalamic-pituitary-adrenal (HPA) axis function also contribute to the neurological complications of diabetes phenotypes. The pathophysiological similarities between diabetes and stress-related mood disorders suggest that common mechanistic mediators may be involved in the etiology and progression of the neurological complications of these disorders. When combined with the accumulating evidence from pre-clinical models, these data support the hypothesis that a long-term consequence of diabetes/obesity phenotypes is accelerated brain aging that results in neuropsychological deficits and increased vulnerability to co-morbidities such as depressive illness.

Introduction

Ongoing epidemiological studies by the Centers for Disease Control determined that there is a significant increase in the incidence of obesity in the United States. The National Health and Nutrition Examination Survey (NHANES) estimates that greater than 60% of the adult US population may be categorized as either overweight or obese [1•]. These epidemiological results represent an important health-care issue that has profound socio-economic ramifications, especially in view of the complications that may arise from obesity phenotypes, such as insulin resistance and type 2 diabetes. Since current estimates report that one of every four Medicare dollars is spent on the treatment of diabetes, this growing population of diabetic patients will have a significant financial impact on public health costs. There is a growing appreciation that the complications of diabetes extend into the central nervous system (CNS), thereby leading to the development of diabetic encephalopathy and increased risk of neurological co-morbidities. In view of these observations, the goals of this review will be: 1) to discuss the impact of hyperglycemia and insulin resistance upon the structure and function of the hippocampus, a brain region that serves as a critical integration center for learning and memory in the mammalian brain; and 2) describe how deficits in hippocampal synaptic

Address for Correspondence: Lawrence P. Reagan, Ph.D., Department of Pharmacology, Physiology and Neuroscience, School of Medicine, University of South Carolina, 6439 Garners Ferry Rd, Columbia, SC 29208 USA, Phone: 001 803 733-3219, Fax: 001 803 733-1523, E-mail: lpreagan@med.sc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

plasticity in diabetic subjects may adversely affect cognitive performance and increase neuronal vulnerability for stress-related disorders like depressive illness.

Is accelerated brain aging a consequence of diabetes?

The accumulated data from experimental models of diabetes suggest that a consequence of chronic hyperglycemia is accelerated brain aging, as proposed by Gispen, Biessels and co-workers [2]. Examples include neuroanatomical alterations, neurochemical changes, impairments in stress reactivity and HPA axis activity, as well as deficits in plasticity and insulin signaling, all of which may contribute to cognitive/behavioral deficits. For example, streptozotocin (STZ) diabetic rats, an experimental model of type 1 diabetes, rapidly exhibit dendritic remodeling in the CA3 region of the rat hippocampus [3]. Subsequent studies determined that hyperglycemia mediated morphological changes are more widespread in the hippocampus of STZ rats and include redistribution of synaptic proteins that may affect neurotransmission and plasticity [4]. An important consideration, especially in relation to hippocampal function, is whether these neuroanatomical changes represent the initiation of irreversible neuronal damage in diabetic subjects. Neuronal apoptosis and suppression of cell proliferation/neurogenesis are observed in the hippocampus of diabetic rodents [5-8], albeit under conditions of uncontrolled hyperglycemia. As such, the relationship of these findings to the clinical situation in which patients attempt to maintain tight glycemic control remains to be determined. Indeed, previous studies illustrated that diabetes-induced morphological changes in the hippocampus [9], as well as deficits in hippocampal synaptic plasticity [10], are reversed with insulin replacement. Nonetheless, neuronal loss and apoptosis following extended periods of hyperglycemia are suggestive of increased neuronal vulnerability that may have additive or synergistic effects when combined with the other neurological complications of diabetes.

Insulin receptor expression and signaling: correlation with cognitive function

The insulin receptor (IR) is expressed in discrete neuronal populations in the CNS, including the hippocampus [11,12], where it is proposed to participate cognitive function [13]. Insulin improves cognitive performance in humans and animals in a wide variety of settings, including healthy subjects [14-16], aged subjects [17-19], Alzheimer's disease (AD) patients [20-22] and in experimental models of insulin resistance [23]. Additionally, spatial learning of a hippocampal-dependent task, namely the Morris water maze, increases IR expression and signaling [24]. Physiologically-relevant increases in plasma insulin levels also stimulates the translocation of the insulin-sensitive glucose transporter GLUT4 to the plasma membrane in the rat hippocampus [25]. These data support the hypothesis that activation of insulin receptor signaling cascades improves cognitive/behavioral performance. The data regarding the relationship between insulin receptor activity and behavioral performance in experimental models of diabetes is less consistent. In experimental models of type 1 diabetes, STZ diabetic rats exhibit behavioral deficits in the water maze task that are associated with impairments in hippocampal long-term potentiation (LTP), a cellular correlate of learning and memory [10]. Conversely, other studies have failed to demonstrate deficits in water maze performance in hypoinsulinemic Akita mice [26]. These disparate findings may be related to the type of analyses performed since a study by Zhao and co-workers determined that STZ diabetic rats performed as well as non-diabetic controls in some aspects of water maze performance, but more poorly in others [27•]. Hippocampal IR expression [27], as well as plasma membrane association of GLUT4 [25], is reduced in STZ rats, suggesting that impairments in hippocampal IR expression and signaling contributes to deficits in hippocampal-dependent tasks. Interestingly, behavioral training strengthens IR signaling in the diabetic rat hippocampus [27], providing further evidence that at least some of the neurological complications of hyperglycemia represent plastic, not permanent, changes.

Analyses of behavioral performance and hippocampal synaptic plasticity in experimental models of type 2 diabetes have also yielded inconsistent findings, with some studies suggesting that water maze performance and hippocampal LTP are reduced [28], while others report that these measures are unaffected [29]. One important caveat associated with these studies is that performance in the water maze is dependent upon loco-motor activity, which may be adversely affected in diabetic animals that display decreases in muscle mass (such as type 1 models) or increases in adiposity (such as type 2 models). Evaluation of learning and memory performance in a task that is less dependent upon loco-motor activity, such as the variable interval delayed alternation (VIDA) task, may more directly assess behavioral performance in experimental models of diabetes. In this regard, type 2 Zucker diabetic rats effectively learn the VIDA task when intertrial intervals (ITI) are short. However, when the ITI is lengthened, which is dependent upon intact hippocampal function, behavioral performance deteriorates in the type 2 rats when compared to their lean littermates [30•]; these behavioral deficits in Zucker diabetic rats were associated with decreases in IR signaling. Such results support the hypothesis that decreases in hippocampal IR activities contribute to behavioral deficits in type 2 rodents. Nonetheless, the ‘take-home-message’ from these pre-clinical studies is that a variety of factors may impact the outcome of behavior and hippocampal plasticity experiments in diabetic animals, ranging from the physiological/pathophysiological characteristics of the animal model to the selection and analysis of the particular behavioral tests.

Translation of animal studies to the clinical setting

One of the most critical questions that remains to be determined is whether these pre-clinical data translate to the clinical setting. The clinical literature that has described structural and functional changes in diabetic patients is somewhat equivocal in that the magnitude and significance of cognitive deficits in diabetic patients is a subject of debate. Neuroanatomical abnormalities have been reported in type 1 and type 2 patients (For review see [31]) and the advent of imaging technologies has confirmed and extended these previous observations. For example, while MRI techniques have not identified cerebral or hippocampal atrophy in type 1 patients [32,33], voxel-based morphometry (VBM) revealed decreases in grey matter density in type 1 patients [34]. Imaging studies in type 2 patients have yielded more consistent findings suggestive of cerebral atrophy, in that MRI analyses have identified structural atrophy [35], particularly in the limbic structures such as the hippocampus and amygdala [36]. Decreases in hippocampal formation volume in type 2 patients have also been identified using a combined MRI/VBM approach [37•]. Importantly, these structural changes are often associated with neuropsychological deficits in type 2 patients [35,37].

The complexity of the pathophysiological causes and consequences of diabetes may contribute to the dissimilar findings in clinical studies. For example, a variety of factors have been proposed to negatively influence the structural and functional integrity of the brain in diabetes patients, including the degree of glycemic control, the number and severity of hypoglycemic episodes, the age of onset and the duration of diabetes (For reviews, see [38,39]). A consequence of these metabolic deficits is impairments in HPA axis function, which may further exacerbate the neurological complications of diabetes. Indeed, impairments in HPA axis function and elevated basal GCs are implicated in the neurological complications observed of type 1 and type 2 diabetic animals [3,30,40-42]. Clinical studies have yielded inconsistent findings regarding HPA axis activity in diabetic patients, although a recent study by Convit and co-workers demonstrated an association between glycemic control, HPA axis dysfunction and cognitive performance in type 2 diabetes patients [43•].

Some investigators suggest that CNS structural and functional deficits in diabetic patients are subtle and do not represent a significant cognitive burden in diabetic individuals compared to the general population. Irrespective of the ‘significance’ of cognitive impairments identified

in diabetes, the life-long complications of hyperglycemia predispose diabetic patients to co-morbidities such as dementia, AD and recurrent depressive illness [44-46]. For instance, epidemiological studies suggest that diabetic patients are two to three-fold more likely to develop depressive illness when compared to non-diabetic individuals [47•]. It is interesting to note that there are striking similarities between the neurological consequences of diabetes and depressive illness, including decreases in hippocampal formation volume [46]. In addition to HPA axis dysfunction and hypercortisolemia, a variety of other endocrine factors may predispose diabetic patients to depressive illness, including elevations in plasma leptin levels and/or leptin resistance (as in type 2 diabetes) and increased plasma levels of pro-inflammatory cytokines [48•]. Indeed, cytokines are implicated in the pathogenesis of type 1 diabetes and the progression of type 2 diabetes. Therefore, while the magnitude of cognitive deficits observed in diabetic subjects may remain a subject of debate, the significance of the underlying neuroendocrinological, neurophysiological and neuroanatomical changes that may ultimately produce cognitive deficits and co-morbidities in diabetes subjects should not be overlooked or marginalized.

Conclusions

The long-term consequences of hyperglycemia upon the CNS are an important health care issue in view of the growing obesity and diabetes patient populations. While clinical and pre-clinical studies have failed to reach a consensus, the accumulated data suggest that the neurological complications of diabetes include deficits include hippocampal synaptic plasticity, as well as structural and cognitive deficits. Less debate surrounds the increased incidence of co-morbidities in diabetic patients, including increased risk for Alzheimer's disease [49] and depressive illness [47•]. As a result, diabetic encephalopathy could surpass renal failure, heart disease and retinopathy as the major complication of diabetes. The good news for diabetic patients is the emergence of innovative transplantation strategies and pharmacological treatments that have the potential to significantly reduce or eliminate diabetes-related complications. These include new approaches to enhance current pancreatic islet cell transplantation strategies for type 1 patients [50••], as well as the advancement of novel drug strategies such as insulin mimetics [51] and incretin mimetics [52] for the treatment of type 2 diabetes and obesity. When combined with lifestyle changes, including diet and exercise, these developing technologies offer hope to clinicians and patients for the successful treatment of the neurological consequences of diabetes and obesity.

Acknowledgements

The author's work is supported in part by Juvenile Diabetes Research Foundation grant number 2-03-675, NIH grant number NS047728 and the University of South Carolina Research Foundation.

Reference List

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 2006;295:1549-1555. [PubMed: 16595758] The National Health and Nutrition Examination Survey (NHANES) revealed that increasing numbers of children and adolescence may be categorized as overweight. Additionally, greater than 60% of the adult US population may be defined as either overweight or obese.
2. Kamal A, Biessels G-J, Duis SEJ, Gispen WH. Learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: interaction of diabetes and ageing. *Diabetologia* 2000;43:500-506. [PubMed: 10819245]
3. Magariños AM, McEwen BS. Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. *Proc Natl Acad Sci USA* 2000;97:11056-11061. [PubMed: 11005876]

4. Grillo CA, Piroli GG, Wood GE, Reznikov LR, McEwen BS, Reagan LP. Immunocytochemical analysis of synaptic proteins provides new insights into diabetes-mediated plasticity in the rat hippocampus. *Neuroscience* 2005;136:477–486. [PubMed: 16226381]
5. Kim HB, Jang MH, Shin MC, Lim BV, Kim YP, Kim KJ, Kim EH, Kim CJ. Treadmill exercise increases cell proliferation in dentate gyrus of rats with streptozotocin-induced diabetes. *J Diabetes Complications* 2003;17:29–33. [PubMed: 12505754]
6. Beauquis J, Roig P, Homo-Delarche F, De Nicola A, Saravia F. Reduced hippocampal neurogenesis and number of hilar neurones in streptozotocin-induced diabetic mice: reversion by antidepressant treatment. *Eur J Neurosci* 2006;23:1539–1546. [PubMed: 16553617]
7. Saravia FE, Beauquis J, Revsin Y, Homo-Delarche F, de Kloet ER, De Nicola AF. Hippocampal neuropathology of diabetes mellitus is relieved by estrogen treatment. *Cell Mol Neurobiol* 2006;26:943–957. [PubMed: 16807785]
8. Li ZG, Zhang W, Grunberger G, Sima AA. Hippocampal neuronal apoptosis in type 1 diabetes. *Brain Res* 2002;946:221–231. [PubMed: 12137925]
9. Magariños AM, Jain K, Blount ED, Reagan L, Smith BH, McEwen BS. Peritoneal implantation of microencapsulated porcine pancreatic islets in diabetic rats ameliorates severe hyperglycemia and prevents retraction and simplification of hippocampal dendrites. *Brain Res* 2001;902:282–287. [PubMed: 11384623]
10. Biessels G-J, Kamal A, Urban IJ, Spruijt BM, Erkelens DW, Gispen WH. Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment. *Brain Res* 1998;800:125–135. [PubMed: 9685609]
11. Marks JL, Porte D Jr, Stahl WL, Baskin DG. Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology* 1991;127:3234–3236. [PubMed: 2249648]
12. Doré S, Kar S, Rowe W, Quirion R. Distribution and levels of [¹²⁵I]IGF-I, [¹²⁵I]IGF-II and [¹²⁵I] Insulin receptor binding sites in the hippocampus of aged memory-unimpaired and -impaired rats. *Neuroscience* 1997;80:1033–1040. [PubMed: 9284058]
13. Park CR. Cognitive effects of insulin in the central nervous system. *Neurosci Biobehav Rev* 2001;25:311–323. [PubMed: 11445137]
14. Kopf SR, Baratti CM. Memory-improving actions of glucose: involvement of a central cholinergic muscarinic mechanism. *Behav Neur Biol* 1994;62:237–243.
15. Parkes M, White KG. Glucose attenuation of memory impairments. *Behav Neurosci* 2000;114:307–319. [PubMed: 10832792]
16. Park CR, Seely RJ, Craft S, Woods SC. Intracerebroventricular insulin enhances memory in a passive-avoidance task. *Physiol Behav* 2000;68:509–514. [PubMed: 10713291]
17. Winocur G, Gagnon S. Glucose treatment attenuates spatial learning and memory deficits of aged rats on tests of hippocampal function. *Neurobiol Aging* 1998;19:233–241. [PubMed: 9661998]
18. Messier C, Gagnon M, Knott V. Effect of glucose and peripheral glucose regulation on memory in the elderly. *Neurobiol Aging* 1997;18:297–304. [PubMed: 9263195]
19. Manning CA, Stone WS, Korol DL, Gold PE. Glucose enhancement of 24-h memory retrieval in healthy elderly humans. *Behav Brain Res* 1998;93:71–76. [PubMed: 9659988]
20. Messier C, Gagnon M. Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. *Behav Brain Res* 1996;75:1–11. [PubMed: 8800646]
21. Manning CA, Ragozzino ME, Gold PE. Glucose enhancement of memory in patients with probable senile dementia of the Alzheimer's type. *Neurobiol Aging* 1993;14:523–528. [PubMed: 8295654]
22. Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD, Cherrier M, Lofgreen C, Latendresse S, Petrova A, Plymate S, Raskind M, Grimwood K, Veith RC. Enhancement of memory in Alzheimer Disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* 1999;56:1135–1140. [PubMed: 10591291]
23. Greenwood CE, Winocur G. Glucose treatment reduces memory deficits in young adult rats fed high-fed diets. *Neurobiol Learn Mem* 2001;75:179–189. [PubMed: 11222059]
24. Zhao W, Chen H, Moore E, Meiri N, Quon MJ, Alkon DL. Brain insulin receptors and spatial memory. *J Biol Chem* 1999;274:34893–34902. [PubMed: 10574963]
25. McEwen BS, Reagan LP. Glucose transporter expression in the central nervous system: relationship to synaptic function. *Eur J Pharmacol* 2004;490:13–24. [PubMed: 15094070]

26. Choeiri C, Hewitt K, Durkin J, Simard CJ, Renaud JM, Messier C. Longitudinal evaluation of memory performance and peripheral neuropathy in the Ins2C96Y Akita mice. *Behav Brain Res* 2005;157:31–38. [PubMed: 15617768]
27. Dou JT, Chen M, Dufour F, Alkon DL, Zhao WQ. Insulin receptor signaling in long-term memory consolidation following spatial learning. *Learn Mem* 2005;12:646–655. [PubMed: 16287721]
Streptozotocin (STZ) diabetic rats display some subtle performance deficits compared to control rats, which may explain the discrepancies in studies that have examined water maze performance in STZ rats. Behavioral training elicited increases in insulin receptor signaling in the hippocampus of STZ rats, suggesting that diabetes-induced deficits in insulin signaling represent plastic, not irreversible, changes.
28. Li XL, Aou S, Oomura Y, Hori N, Fukunaga K, Hori T. Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents. *Neuroscience* 2002;113:607–615. [PubMed: 12150780]
29. Belanger A, Lavoie N, Trudeau F, Massicotte G, Gagnon S. Preserved LTP and water maze learning in hyperglycaemic-hyperinsulinemic ZDF rats. *Physiol Behav* 2004;83:483–494. [PubMed: 15581671]
30. Winocur G, Greenwood CE, Piroli GG, Grillo CA, Reznikov LR, Reagan LP, McEwen BS. Memory Impairment in Obese Zucker Rats: An Investigation of Cognitive Function in an Animal Model of Insulin Resistance and Obesity. *Behav Neurosci* 2005;119:1389–1395. [PubMed: 16300445] Type 2 Zucker diabetic rats performed more poorly in the variable interval delayed alternation task when compared to their lean littermates, behavioral deficits that were associated with impaired insulin receptor signaling. These results strengthen the relationship between insulin signaling and memory and emphasize the importance of test selection when evaluating behavioral performance in diabetic rodents.
31. Reagan LP. Glucose, stress and hippocampal neuronal vulnerability. *Int Rev Neurobiol* 2002;51:289–324. [PubMed: 12420363]
32. Lobnig BM, Kromeke O, Optenhostert-Porst C, Wolf OT. Hippocampal volume and cognitive performance in long-standing Type 1 diabetic patients without macrovascular complications. *Diabet Med* 2006;23:32–39. [PubMed: 16409563]
33. Ferguson SC, Blane A, Perros P, McCrimmon RJ, Best JJ, Wardlaw J, Deary IJ, Frier BM. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. *Diabetes* 2003;52:149–156. [PubMed: 12502506]
34. Musen G, Lyoo IK, Sparks CR, Weinger K, Hwang J, Ryan CM, Jimerson DC, Hennen J, Renshaw PF, Jacobson AM. Effects of type 1 diabetes on gray matter density as measured by voxel-based morphometry. *Diabetes* 2006;55:326–333. [PubMed: 16443764]
35. Manschot SM, Brands AM, van der GJ, Kessels RP, Algra A, Kappelle LJ, Biessels GJ. Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. *Diabetes* 2006;55:1106–1113. [PubMed: 16567535]
36. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia* 2003;46:1604–1610. [PubMed: 14595538]
37. Gold SM, Dziobek I, Sweat V, Tirsi A, Rogers K, Bruehl H, Tsui W, Richardson S, Javier E, Convit A. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* 2007;50:711–719. [PubMed: 17334649]
38. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. *Pediatr Diabetes* 2006;7:289–297. [PubMed: 17054452]
39. Ryan CM. Memory and metabolic control in children. *Diabetes Care* 1999;22:1239–1241. [PubMed: 10480763]
40. Leedom LJ, Meehan WP, Zeidler A. Avoidance responding in mice with diabetes mellitus. *Physiol Behav* 1987;40:447–451. [PubMed: 2819907]
41. Scribner KA, Walker CD, Cascio CS, Dallman MF. Chronic streptozotocin diabetes in rats facilitates the acute stress response without altering pituitary or adrenal responsiveness to secretagogues. *Endocrinology* 1991;129:99–108. [PubMed: 1647314]

42. Oster MH, Castonguay TM, Keen CL, Stern JS. Circadian rhythm of corticosterone in diabetic rats. *Life Sci* 1988;43:1643–1645. [PubMed: 3193850]
43. Bruehl H, Rueger M, Dziobek I, Sweat V, Tirsi A, Javier E, Arentoft A, Wolf OT, Convit A. Hypothalamic-pituitary-adrenal axis dysregulation and memory impairments in type 2 diabetes. *J Clin Endocrinol Metab* 2007;92:2439–2445. [PubMed: 17426095]
44. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53:1937–1942. [PubMed: 10599761]
45. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: does cortisol play a role? *Biol Psychiatry* 2004;55:1–9. [PubMed: 14706419]
46. McEwen BS, Magarinos AM, Reagan LP. Studies of hormone action in the hippocampal formation: possible relevance to depression and diabetes. *J Psychosom Res* 2002;53:883–890. [PubMed: 12377298]
47. Lustman PJ, Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. *J Diabetes Complications* 2005;19:113–122. [PubMed: 15745842] Epidemiological studies suggest that diabetes patients are more than two-fold more likely to develop depressive illness when compared with the general population. Diabetic patients with this co-morbidity may experience more severe symptomatology, including increased risk of relapse. The degree of metabolic control maintained by diabetes patients appears to be an important contributor to the development of this co-morbidity.
48. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006;27:24–31. [PubMed: 16316783] Emerging evidence suggests an important link between increased productions of inflammatory mediators such as pro-inflammatory cytokines and neurochemical/neurotrophic changes in the brain. As such, cytokines and their interactions with stress hormones may participate in the etiology and/or progression of depressive illness.
49. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res* 2007;4:147–152. [PubMed: 17430239]
50. Merani S, Shapiro AM. Current status of pancreatic islet transplantation. *Clin Sci (Lond)* 2006;110:611–625. [PubMed: 16689680] The success of the Edmonton protocol established renewed enthusiasm for pancreatic islet transplantation for the treatment of type 1 diabetes. Emerging technologies for islet survival and islet donors, including porcine islets, as well as advances in immunosuppression strategies, may permit many type 1 patients achieve insulin independence.
51. Air EL, Strowski MZ, Benoit SC, Conarello SL, Salituro GM, Guan XM, Liu K, Woods SC, Zhang BB. Small molecule insulin mimetics reduce food intake and body weight and prevent development of obesity. *Nat Med* 2002;8:179–183. [PubMed: 11821903]
52. Cohen A, Horton ES. Progress in the treatment of type 2 diabetes: new pharmacologic approaches to improve glycemic control. *Curr Med Res Opin* 2007;23:905–917. [PubMed: 17407648]