A subset of traumatic brain injury (TBI) patients exhibit cognitive deficits later in life which may be due to the underlying pathology associated with Alzheimer’s disease (AD) or chronic traumatic encephalopathy. The similarities between chronic traumatic encephalopathy and AD merit investigation of potentially similar mechanisms underlying the two diseases. Experimental and clinical studies of AD brains have revealed that insulin resistance links metabolic dysfunction to the neurodegeneration and cognitive deficits associated with AD. Recent work in experimental TBI has established that recovery is dependent on the return of normal brain metabolism and mounting evidence for a role of brain insulin in regulating central metabolism suggests that TBI, like AD, results in central insulin resistance. Here, we review the converging evidence from AD, TBI and diabetes research linking insulin insensitivity to neurodegeneration.

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**Traumatic brain injury**

Traumatic brain injuries (TBIs) are increasingly recognized as an important global health concern and represent the leading cause of disability and death worldwide [1]. In the USA alone, there are, on average, 2.5 million documented head injuries annually, although the true number probably far exceeds that value [2]. The estimated economic costs of TBI (in 2000 dollars) approaches US$60 billion including healthcare costs and lost productivity [3]. At least 5.3 million Americans (nearly 2% of the total population) are living with long-term disability associated with TBI [4]. In addition, there is mounting evidence that individual, and in particular, repeated head injuries greatly increase the possibility of other diseases and disabilities, further increasing the overall societal costs [5]. These epidemiological data indicate the importance of both TBI prevention and the development of treatment and rehabilitation strategies for this population. By definition, TBI involves an external mechanical force that causes brain dysfunction. Broadly, TBI can be divided into two categories, focal injuries due to contusions, lacerations, penetrating ballistic objects or intracranial hemorrhage and diffuse injuries that typically occur after impact acceleration or explosive blasts [6]. The biomechanical forces associated with these two types of injuries are obviously very different. Furthermore, head injuries are extremely heterogeneous and outcomes can vary dramatically based on the severity of impact, age, comorbidities and genetics among other variables. Therefore, TBI is really a broad diagnosis that includes a large number of mechanical head injuries; however, all CNS trauma outcomes are determined by both primary and secondary phases of damage. Primary inju-
TBI rapidly disrupts neuronal homeostasis. The mechanical deformation of brain tissue can result in membrane shearing, neuronal death, rapid and spreading depolarization, increases in excitatory amino acid release and axonal disconnections [8,9]. In the first few minutes after TBI, neuronal survival is dependent on a rapid restoration of membrane potentials and ionic homeostasis. If cells cannot rapidly repolarize their membranes, the resulting ionic imbalances can lead to swelling and lysis of neurons, neurites and glia [7].

Thus, control of inflammatory responses is critical to TBI outcomes but is energetically expensive. This crisis situation is often exacerbated by hemorrhages, impairments in cerebral perfusion and autoregulation, and diminished neuronal capacity to utilize energy. Over time after the initial injury, metabolic dysfunction and inflammatory responses mutually reinforce one another. The goals of this article are to review the literature on the role of central metabolic dysfunction in TBIs and further discuss how this process affects long-term outcomes following TBI.

**Cerebral metabolism after TBI**

The pathophysiology of TBI is complex, but involves diffuse axonal injury, frank neuronal death, inflammation, and persistent metabolic abnormalities. There is a consistent phenomenon across brain injury subtypes that the capacity for the brain to utilize energy (namely glucose) is significantly modulated following injury. Most studies have reported a transient period of hypermetabolism followed by a prolonged hypometabolic phenotype [10–12]. This phenomenon has been reported in both animal and human studies. The initial hypermetabolism is apparently in response to the release of excitatory amino acids immediately following injury and may be necessary to recover some aspects of homeostasis in the injured brain [10]. In an effort to investigate the role of metabolic dysfunction as a mediator of enhanced vulnerability to repeated injury after TBI, we recently identified that a single impact (weight drop) led to a significant increase in brain glucose utilization in mice by postinjury day 6, and by 10 days brain glucose utilization dropped below baseline and remained low through the latest time point examined (20 days). On the other hand, in mice injured twice, 3 days apart, no significant change in brain glucose utilization was observed at any time point examined, indicating an inability of the brain to meet increased metabolic demands. Finally, if the two injuries occurred further apart (20 days apart), the pattern of increased glucose utilization after the second impact paralleled the increase that occurred after just one impact. These data suggest that a longer recovery period between impacts corresponds to an enhanced ability of the brain to mount the appropriate metabolic response to the second injury. This pattern of glucose utilization was associated with cognitive function after injury, with the group injured twice (3 days apart) exhibiting the greatest learning/memory deficits, while the other groups recovered cognitive function over time [13]. Thus, the acute period following TBI can be conceptualized as a metabolic crisis, wherein the energetic demands on the injured brain are increased to allow for rapid recovery. In severe or repeated TBI, there is simultaneously the need to maintain cellular integrity in the face of excess glutamate release and mechanical injury to the cell membranes, and a reduced capacity to utilize energetic substrates, resulting in a reduced capacity for tissue repair and functional recovery. The recovery of cognitive and executive function correlates strongly with the return of normal glucose metabolism in both humans and animals [13–15], however, few studies have definitively linked alterations in glucose metabolism to functional outcome following TBI.

Until relatively recently, energy metabolism inside the CNS was not believed to be regulated in an insulin-dependent manner, and in fact CNS cells were thought to be devoid of insulin all together. It is now well understood that insulin is both transported into the CNS across the blood–brain barrier and synthesized locally [16–18]. Moreover, brain insulin receptors are densely distributed throughout the brain, including the olfactory bulbs, cerebral cortex, hippocampus, hypothalamus, amygdala and septum [19]. Insulin receptor signaling in the CNS differs from that in peripheral tissues in that insulin does not directly upregulate glucose transporter gene expression in neurons and thus does not directly increase neuronal glucose uptake. Rather, insulin modulates neuronal physiology via MAPK and PI3K signaling [20], which in turn alter aspects of metabolism and promote neuronal regeneration and survival via phosphorylation of Akt. Insulin receptor sensitivity is regulated in two general ways. First, ligand-dependent receptor activation induces phosphorylation of the IRS-1 protein [21]. Phosphorylation at specific epitopes reduces the interaction between IRS-1 and the membrane-bound insulin receptor and prevents further signaling [22]. This is a homeostatic negative feedback system to regulate cellular responses to insulin [23].
ligand-independent manner [24,25]. In particular, the proinflammatory cytokine TNF-α provides a clear mechanistic link between acute trauma-induced neuroinflammation and metabolic dysfunction [26–29]. A primary (though not exclusive) regulator of TNF-α-induced inflammatory responses is the transcription factor NF-κB, which has been shown to be involved in the etiology of insulin resistance and Type 2 diabetes [30]. TNF-α and other inflammatory processes also promote IRS-1 phosphorylation via activation of the JNK pathway [31]; for in-depth reviews, see [28,32,33]. In addition to the direct effects of neuroinflammation, TBI also produces widespread axon degeneration [34]. Both insulin and IGF-1 are known to play a significant role in the regulation of myelin synthesis [35,36], and treatment with IGF-1 has been shown to protect oligodendrocytes in animal models of excitotoxicity and cerebral hypoxia-ischemia [37,38]. Taken together, the relationship between TBI-induced neuroinflammation and the resulting pathophysiology/cognitive deficits are likely mediated in part by the direct disruption of central metabolic processes (Figure 1).

Disregulation of metabolic processes is detrimental to TBI recovery [39]. Hyperglycemia at the time of hospital admission is associated with poor outcome and greater mortality rates in TBI patients [40,41]. Not surprisingly, recent clinical reports reveal that obese TBI patients (who commonly present with insulin resistance in the form of Type 2 diabetes) experience more complications (i.e., multiple organ system failure, acute respiratory distress syndrome, myocardial infarction and deep vein thrombosis) and require longer hospital stays and more medical interventions (i.e., mechanical ventilation, dialysis) compared with nondiabetic controls [42]. Diabetes is also a significant predictor for mortality after TBI [43]. Several clinical trials targeting glucose control in TBI patients have been conducted. Early results indicate some improvement with intensive insulin therapy at the time of hospitalization: some studies link insulin treatment to reduced infection rates and shorter hospitalizations, however, results have been mixed and mortality rate, particularly among severe TBI patients, does not improve with intensive insulin therapy [44–46]. Nonetheless, in animal models, insulin is well understood to be a potent neuroprotectant that can promote neuronal survival and recovery following a variety of insults to the CNS [47,48]. In rats, treatment with insulin or IGF-1 attenuates ischemic brain damage [49] in addition to improving motor and cognitive recovery following TBI [50]. Such patterns of recovery can be attributed in part to the role of IGF-1 as a regulator of neuronal growth and differentiation, as well as its ability to promote synaptic plasticity and neurogen-

![Figure 1. Neuroinflammation and insulin resistance in the CNS.](image) Inflammatory events, such as those induced by traumatic brain injury, activate signaling cascades (including NF-κB and JNK) that phosphorylate and inactivate insulin receptor substrate proteins. Inactivation of insulin receptor substrate proteins, in turn, prevents insulin receptor signaling. One prominent downstream target of insulin signaling is AKT, a neuroprotective kinase that also influences neuronal energy metabolism. Insulin resistance following traumatic brain injury therefore deprives the nervous system of this protective pathway, rendering the individual vulnerable to neurodegeneration and cognitive deficits.

Cognitive decline after TBI

Repeated TBI is closely linked both pathophysiologically and epidemiologically to chronic neurodegenerative disease. For instance, cognitive disabilities following TBI vary largely based on severity, age and general health of the individual, and the degree of cognitive impairment following a single TBI ranges from mild temporary cognitive impairment to Alzheimer’s-like cognitive deterioration. Both the number of lifetime
TBI. Coupled with reports of increasing TBI rates in both male and female athletes, members of the armed forces and other civilians, there is now a greater need than ever to identify the mechanisms underlying trauma-induced cognitive decline.

Individuals that have experienced repetitive concussive or subconcussive brain injury are at an increased risk of developing a neurodegenerative disorder called chronic traumatic encephalopathy (CTE), which closely resembles AD [63]. Acute symptoms of CTE manifest as confusion, mild memory loss, reduced concentration and attention as well as dizziness and headaches. Over time these symptoms progress to the point of overt dementia, including lack of insight and poor judgment, language difficulty, aggression and irritability [64]. This cluster of symptoms had been historically described in boxers as ‘punch drunk’ [65] or ‘dementia pugilistica’ [66], and is today recognized as a serious consequence of repeated brain trauma in athletes, members of the military and law enforcement and even victims of physical abuse [67–69]. The presentation of CTE is distinct from other trauma-related symptoms of cognitive decline (i.e., postconcussion syndrome) in that, like AD, CTE is a neurodegenerative disease. Characteristic pathological features of CTE include tau-positive neurofibrillary tangles along superficial frontal and temporal cortices, in sulci, and along the neurovascu-
motes amyloidosis [95,96], likewise amyloid-β production has been shown to promote insulin resistance [97,98]. Finally, transgenic animals that lack brain IRS-2 [99], insulin [100] or neuron-specific insulin receptors [101] display hyperphosphorylation of tau and neuroinflammation, increased cell death, and cognitive deficits.

Taken together, the epidemiological and clinical research are uncovering concrete evidence of a relationship between AD and insulin resistance [102,103]. Indeed, the relationship between insulin signaling and AD may turn out to be not just a therapeutic target but also an early detection marker for AD [104]. Moreover, the recent surge of interest in central insulin signaling has identified a role for insulin dysfunction in the pathophysiology of additional neurodegenerative diseases, including vascular dementia [105,106], Parkinson’s [107] and Huntington’s diseases [108], thus potentially uncovering a novel therapeutic approach. As mentioned above, direct insulin treatment is undesirable for this group of disease states given the potential for creating a state of hypoglycemia and reduced efficacy as a function of insulin resistance associated with neurodegenerative disease. However, a few clinical trials using intranasal insulin administration have reported successful cognitive outcomes in AD or mild cognitive impairment patients [109–111]. However, pharmacological approaches aimed at enhancing insulin receptor sensitivity have seen success in neurodegenerative diseases. One such class of drugs includes PPAR-γ agonists, which significantly improve insulin sensitivity by increasing the production of glucoregulatory proteins [112]. Selective PPAR-γ agonists, such as rosiglitazone and pioglitazone, improve cognitive performance and reduce amyloid-β in patients with mild AD [113,114], and produce promising behavioral and neuroprotective effects in animal models of Parkinson’s disease [115], amyotrophic lateral sclerosis [116] and Huntington’s disease [117]. Follow-up clinical trials using PPAR-γ agonists in mild-to-moderate AD have had minimal success owing in part to variability in the progression of AD and small sample sizes. Thus, although these drugs are generally well tolerated and have a good safety profile, their use is not widely recommended for the treatment of AD [118–120]. Similar pharmacologic approaches have recently been successfully implemented in animal models of TBI. For example, the incretin GLP-1 is a peptide that controls blood glucose [121]. Through its action on the GLP-1 receptor (GLP-1R), GLP-1 promotes pancreatic β-cell proliferation, inhibits β-cell apoptosis and increases insulin secretion [121,122]. Importantly, GLP-1Rs are expressed throughout the brain and central GLP-1 can both control whole-body insulin sensitivity [123] and promote neuroprotection [124]. Heile et al. [125] transplanted GLP-1 transfected mesenchymal stem cells into the lateral ventricles of rats prior to TBI. The encapsulated stem cells produced GLP-1 throughout the duration of the experiment, and significantly reduced cell death and neuroinflammation [125]. Incretin mimetics represent a promising treatment strategy for AD and have been shown to improve neuronal plasticity through mechanisms involving normalization of neuronal metabolic activity [126,127]. The GLP-1R agonist, exendin-4, inhibits the development of insulin resistance in a mouse model of AD [128]. Exendin-4 was also recently used in a mouse model of mild TBI: whether administered prior to or following the TBI, treated animals exhibited improved visual and spatial memory relative to controls [129–131]. A clinical trial on the effects of liraglutide (a GLP-1 receptor agonist) on cognition and neurodegeneration in AD patients is currently underway [132]. Taken together, these studies add to the growing and compelling evidence of the contribution that insulin sensitivity may have in mediating both TBI-induced pathophysiology and the resulting cognitive deficits.

TBI in both clinical and experimental populations is associated with a temporary but significant derangement of metabolic function. This impairment in brain energy metabolism appears to correlate temporally with both enhanced vulnerability to repeated injury and recovery from the initial insult. Given the relationship between AD and TBI, it seems plausible to propose that mechanical injuries to the nervous system induce long-lasting events in the brain that recapitulate some of the pathophysiology of AD neurodegeneration. These events, including inflammation, impairment in the utilization of metabolic fuels and the development of tau deposits, bear striking similarity to the neurodegenerative process that results in AD. Therefore, understanding the pathophysiology that links TBI to AD or CTE, with a particular focus on energy metabolism, is likely to have significant benefits for both conditions as well as potentially providing biomarkers to guide clinicians in return-to-work/play decisions in TBI.

**Conclusion & future perspective**

Despite significant progress in identifying the signs of and treating overt symptoms of TBI, clinicians and researchers continue to struggle with the long-term consequences of repeated and severe brain injuries. The neuropathology and associated cognitive deficits following TBI are well described as they relate to injury-induced neuroinflammation, however the development of neurodegenerative disease years after the neuroinflammation has resolved represents a gap in our understanding of the mechanisms by which
this occurs. Long-lasting changes in brain metabolism are now understood to play a significant role in mediating the brain’s ability to recover and regenerate damaged tissue after TBI. A greater understanding of these mechanisms may allow both intervention for the prevention of long-term neurodegeneration, and development of biomarker assays to delineate severity and further inform treatment and rehabilitation strategies.

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Executive summary
- Traumatic brain injuries cause dysregulation of brain glucose metabolism and can result in the development of the neurodegenerative disease chronic traumatic encephalopathy.
- Similar neurodegenerative diseases, such as Alzheimer’s disease, are associated with central metabolic dysfunctions mediated by the development of brain insulin resistance.
- Pharmacological reinstatement of brain insulin sensitivity can rescue both neuronal damage and cognitive deficits in rodent models of experimental traumatic brain injury.

References
1 Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 7(8), 728–741 (2008).
2 Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. J. Head Trauma Rehabil. 21(5), 375–378 (2006).
3 Finkelstein EA, Miller TR. The Incidence and Economic Burden of Injuries in the United States. Oxford University Press, New York, NY, USA (2006).
4 Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: a public health perspective. J. Head Trauma Rehabil. 14(6), 602–615 (1999).
5 Plassman BL, Havlik RJ, Steffens DC et al. Documented head injury in early adulthood and risk of Alzheimer’s disease and other dementias. Neurology 55(8), 1158–1166 (2000).
6 Andriessen TM, Jacobs B, Voos PE. Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. J. Cell. Mol. Med. 14(10), 2381–2392 (2010).
7 Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br. J. Anaesth. 99(1), 4–9 (2007).
8 Smith DH, Meaney DF, Shull WH. Diffuse axonal injury in head trauma. J. Head Trauma Rehabil. 18(4), 307–316 (2003).
9 Giza CC, Hovda DA. The new neurometabolic cascade of concussion. Neurosurgery 75(Suppl. 4), S24–S33 (2014).
10 Glenn TC, Kelly DF, Boscardin WJ et al. Energy dysfunction as a predictor of outcome after moderate or severe head injury: indices of oxygen, glucose, and lactate metabolism. J. Cereb. Blood Flow Metab. 23(10), 1239–1250 (2003).
11 Hovda DA, Yoshino A, Kawamata T, Katayama Y, Fineman J, Becker DP. The increase in local cerebral glucose utilization following fluid percussion brain injury is prevented with kynurenic acid and is associated with an increase in calcium. Acta Neurochir. Suppl. (Wien.) 51, 331–333 (1990).
12 Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral conclusion in rats: evidence of a hyper- and subsequent hypometabolic state. Brain Res. 561(1), 106–119 (1991).
13 Weil ZM, Gaiyer KR, Karelina K. Injury timing alters metabolic, inflammatory and functional outcomes following repeated mild traumatic brain injury. Neurobiol. Dis. 70, 108–116 (2014).
14 Lin AP, Liao HJ, Merugumala SK, Prabhu SP, Meehan WP 3rd, Ross BD. Metabolic imaging of mild traumatic brain injury. Brain Imaging Behav. 6(2), 208–223 (2012).
15 Ip EY, Zanier ER, Moore AH, Lee SM, Hovda DA. Metabolic, neurochemical, and histologic responses to vibrissa motor cortex stimulation after traumatic brain injury. J. Cereb. Blood Flow Metab. 23(8), 900–910 (2003).
16 Banks WA. The source of cerebral insulin. Eur. J. Pharmacol. 490(1–3), 5–12 (2004).
17 Gerozissis K. Brain insulin, energy and glucose homeostasis; genes, environment and metabolic pathologies. Eur. J. Pharmacol. 585(1), 38–49 (2008).
18 Van Der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Prog. Neurobiol. 79(4), 205–221 (2006).
19 Hopkins DF, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet. Med. 14(12), 1044–1050 (1997).
20 Ghasemi R, Haeri A, Dargahi L, Mohamed Z, Ahmadiani A. Insulin in the brain: sources, localization and functions. Mol. Neurobiol. 47(1), 145–171 (2013).
21 Gual P, Le Marchand-Brustel Y, Tanti J-FO. Positive and negative regulation of insulin signaling through IRS-1 phosphorylation. Biochimie 87(1), 99–109 (2005).
22 Lima MH, Ueno M, Thirone AC, Rocha EM, Carvalho CR, Saad MJ. Regulation of IRS-1/SHP2 interaction and AKT phosphorylation in animal models of insulin resistance. Endocrine 18(1), 1–12 (2002).

23 Orellana RA, Suryawan A, Kimball SR et al. Insulin signaling in skeletal muscle and liver of neonatal pigs during endotoxemia. Pediatr. Res. 64(5), 505–510 (2008).

24 Schubert M, Brazil DP, Burks DJ et al. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. J. Neurosci. 23(18), 7084–7092 (2003).

25 Freude S, Schilbach K, Schubert M. The role of IGF-1 receptor and insulin receptor signaling for the pathogenesis of Alzheimer’s disease: from model organisms to human disease. Curr. Alzheimer Res. 6(3), 213–223 (2009).

26 Bempho D, You Z, Lo EH, Kim HH, Whalen MJ. TNF alpha and Fas mediate tissue damage and functional outcome after traumatic brain injury in mice. J. Cereb. Blood Flow Metab. 27(11), 1806–1818 (2007).

27 Kadhim HJ, Duchateau J, Sebire G. Cytokines and brain injury: invited review. J. Intensive Care Med. 23(4), 236–249 (2008).

28 Hotamisligil GS. Inflammation and metabolic disorders. Nature 444(7121), 860–867 (2006).

29 Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 389(6651), 610–614 (1997).

30 Arkan MC, Hevener AL, Greten FR et al. IKK-beta links inflammation to obesity-induced insulin resistance. Nat. Med. 11(2), 191–198 (2005).

31 Rui L, Aguirre V, Kim JK et al. Insulin/IGF-1 and TNF-alpha stimulate phosphorylation of IRS-1 at inhibitory Ser307 via distinct pathways. J. Clin. Invest. 107(2), 181–189 (2001).

32 Dandona P, Aljada A. Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol. 25(1), 4–7 (2004).

33 Hotamisligil GS. Inflammatory pathways and insulin action. Int. J. Obes. Relat. Metab. Disord. 27(Suppl. 3), S53–S55 (2003).

34 Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain 136(Pt 1), 28–42 (2013).

35 Ye P, Li L, Richards RG, D’Augustine RP, D’ercole AJ. Myelination is altered in insulin-like growth factor-1 null mutant mice. J. Neurosci. 22(14), 6041–6051 (2002).

36 Chesik D, De Keyser J, Wilczak N. Insulin-like growth factor system regulates oligodendroglial cell behavior: therapeutic potential in CNS. J. Mol. Neurosci. 35(1), 81–90 (2008).

37 Lin S, Fan L-W, Pang Y, Rhodes PG, Mitchell HJ, Cai Z. IGF-1 protects oligodendrocyte progenitor cells and improves neurological functions following cerebral hypoxia-ischemia in the neonatal rat. Brain Res. 1063(1), 15–26 (2005).

38 Ness JK, Wood TL. Insulin-like growth factor I, but not neuretrophin-3, sustains Akt activation and provides long-term protection of immature oligodendrocytes from glutamate-mediated apoptosis. Mol. Cell. Neurosci. 20(3), 476–488 (2002).

39 Oddo M, Schmidt JM, Carrera E et al. Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. Crit. Care Med. 36(12), 3233–3238 (2008).

40 Salim A, Hadizacharia P, Dubose J et al. Persistent hyperglycemia in severe traumatic brain injury: an independent predictor of outcome. Am. Surg. 75(1), 25–29 (2009).

41 Liu-Deryke X, Collingridge DS, Orme J, Roller D, Zurasky J, Hone J. Clinical impact of early hyperglycemia during acute phase of traumatic brain injury. Neurocrit. Care 11(2), 151–157 (2009).

42 Brown CV, Neville AL, Rhee P, Salim A, Velmahos GC. Demetriades D. The impact of obesity on the outcomes of 1,153 critically injured blunt trauma patients. J. Trauma 59(5), 1048–1051; discussion 1051 (2005).

43 Ley EJ, Sour MK, Clond MA et al. Diabetic patients with traumatic brain injury: insulin deficiency is associated with increased mortality. J. Trauma 70(5), 1141–1144 (2011).

44 Yang M, Guo Q, Zhang X et al. Intensive insulin therapy on infection rate, days in NICU, in-hospital mortality and neurological outcome in severe traumatic brain injury patients: a randomized controlled trial. J. Neurosurg. 66(6), 753–758 (2009).

45 Bilotta F, Caramia R, Cernak I et al. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. Neurocrit. Care 9(2), 159–166 (2008).

46 Coester A, Neumann CR, Schmidt MI. Intensive insulin therapy in severe traumatic brain injury: a randomized trial. J. Trauma 68(4), 904–911 (2010).

47 Duarte AI, Santos P, Oliveira CR, Santos MS, Rego AC. Insulin neuroprotection against oxidative stress is mediated by Akt and GSK-3β signaling pathways and changes in protein expression. Biochim. Biophys. Acta 1783(6), 994–1002 (2008).

48 Yu XR, Jia GR, Gao GD, Wang SH, Han Y, Cao W. Neuroprotection of insulin against oxidative stress-induced apoptosis in cultured retinal neurons: involvement of phosphoinositide 3-kinase/Akt signaling pathways and changes in protein expression. Biochim. Biophys. Acta 1783(6), 994–1002 (2008).

49 Hui L, Pei D-S, Zhang Q-G, Guan Q-H, Zhang G-Y. The regulatory mechanism of AKT phosphorylation in animal models of insulin resistance. Curr. Alzheimer Res. 11(2), 151–157 (2014).

50 Saatman KE, Contreras PC, Smith DH et al. Insulin-like growth factor-1 (IGF-1) improves both neurological motor and cognitive outcome following experimental brain injury. J. Neurosci. 27(11), 1052(1), 1–9 (2007).

51 Yuan H, Chen R, Wu L et al. The regulatory mechanism of neurogenesis by IGF-1 in adult mice. Mol. Neurobiol. 51(2), 512–522 (2014).

52 Carlson SW, Madathil SK, Sama DM, Gao X, Shen J, Saatman KE. Conditional overexpression of insulin-like growth factor-1 enhances hippocampal neurogenesis and...
restores immature neuron dendritic processes after traumatic brain injury. *J. Neuropathol. Exp. Neurol.* 73(8), 734–746 (2014).

53 Ponsford JL, Downing MG, Oliver J et al. Longitudinal follow-up of patients with traumatic brain injury: outcome at two, five, and ten years post-injury. *J. Neurotrauma* 31(1), 64–77 (2014).

54 Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer’s disease: the evidence 10 years on; a partial replication. *J. Neurol. Neurosurg. Psychiatry* 74(7), 857–863 (2003).

55 Sundstrom A, Nilsson LG, Cruts M, Adolfsson R, van Broeckhoven C, Nyberg L. Increased risk of dementia following mild head injury for carried but not for non-carriers of the APOE epsilon4 allele. *Int. Psychogeriatr.* 19(1), 159–165 (2007).

56 Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer’s disease. *Neurosci. Biobehav. Rev.* 36(5), 1376–1381 (2012).

57 Arciniegas DB, Held K, Wagner P. Cognitive impairment following traumatic brain injury. *Curr. Treat. Options Neurol.* 4(1), 43–57 (2002).

58 Shear DA, Lu XC, Bombard MC et al. Longitudinal characterization of motor and cognitive deficits in a model of penetrating ballistic-like brain injury. *J. Neurotrauma* 27(10), 1911–1923 (2010).

59 Mah LW, Arnold MC, Graff J. Deficits in social knowledge following damage to ventromedial prefrontal cortex. *J. Neuropsychiatry Clin. Neurosci.* 17(1), 66–74 (2005).

60 Shultz SR, Bao F, Omana V, Chiu C, Brown A, Cain DP. Repeated mild lateral fluid percussion brain injury in the rat causes cumulative long-term behavioral impairments, neuroinflammation, and cortical loss in an animal model of repeated concussion. *J. Neurotrauma* 29(2), 281–294 (2012).

61 Schwarzbold ML, Rial D, De Bem T et al. Effects of traumatic brain injury of different severities on emotional, neuroinflammation, and cortical loss in an animal model of repeated concussion. *J. Neurotrauma* 27(10), 1883–1893 (2010).

62 Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* 130(Pt 10), 2508–2519 (2007).

63 Baugh CM, Stamm JM, Riley DO et al. Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav.* 6(2), 244–254 (2012).

64 Mckee AC, Cantu RC, Nowinski CJ et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J. Neuropathol. Exp. Neurol.* 68(7), 709–735 (2009).

65 Marriott H. Punch Drunk. *JAMA* 91(15), 1103–1107 (1928).

66 Millsap J. Dementia pugilistica. *US Naval Med. Bull.* 35 297–303 (1937).

67 Omalu BI, Hamilton RL, Kamboh MI, Dekosky ST, Bailes J. Chronic traumatic encephalopathy (CTE) in a National Football League Player: Case report and emerging medicolegal practice questions. *J. Forensic Nurs.* 6(1), 40–46 (2010).

68 Goldstein LE, Fisher AM, Tagge CA et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci. Transl. Med.* 4(134), 134ra160 (2012).

69 Roberts GW, Whitlall HL, Acland PR, Bruton CJ. Dementia in a punch-drunk wife. *Lancer* 355(8694), 918–919 (1990).

70 Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol.* 22(2), 142–149 (2012).

71 Mckee AC, Gavett BE, Stern RA et al. TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J. Neuropathol. Exp. Neurol.* 69(9), 918–929 (2010).

72 Stern RA, Riley DO, Daneshvar DH, Nowinski CJ, Cantu RC, Mckee AC. Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. *PM R* 3(Suppl. 2), S460–S467 (2011).

73 Ojo JO, Mouzon B, Greenberg MB, Bachmeier C, Mullan M, Crawford F. Repetitive mild traumatic brain injury augments tau pathology and glial activation in aged hTau mice. *J. Neuropathol. Exp. Neurol.* 72(2), 137–151 (2013).

74 Haj-Ali V, Mohaddes G, Babri SH. Intracerebroventricular insulin improves spatial learning and memory in male Wistar rats. *Behav. Neurosci.* 123(6), 1309–1314 (2009).

75 Zhao WQ, Chen H, Quon MJ, Alkon DL. Insulin and the insulin receptor in experimental models of learning and memory. *Eur. J. Pharmacol.* 490(1–3), 71–81 (2004).

76 Benedict C, Hallschmid M, Hatke A et al. Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* 29(10), 1326–1334 (2004).

77 Bateman JM, McNeill H. Insulin/IGF signalling in neurogenesis. *Cell. Mol. Life Sci.* 63(15), 1701–1705 (2006).

78 Spielman IJ, Little JP, Kliegeris A. Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration. *J. Neuroinmunol.* 273(1–2), 8–21 (2014).

79 Razay G, Wilcock GK. Hyperinsulinaemia and Alzheimer’s disease. *Age Ageing* 23(5), 396–399 (1994).

80 Craft S, Peskind E, Schwartz MW, Schellenberg GD, Raskind M, Porte D Jr. Cerebrospinal fluid and plasma insulin levels in Alzheimer’s disease: relationship to severity of dementia and apolipoprotein E genotype. *Neurology* 50(1), 164–168 (1998).

81 Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. *Diabetes* 51(4), 1256–1262 (2002).

82 Akomolafe A, Beiser A, Meigs JB et al. Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study. *Arch. Neurol.* 63(11), 1551–1555 (2006).

83 De Santi S, De Leon MJ, Rusinek H et al. Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol. Aging* 22(4), 529–539 (2001).
Mosconi L, Pupi A, De Leon MJ. Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer’s disease. *Ann. NY Acad. Sci.* 1147:180–195 (2008).

Arnaiz E, Jelic V, Almquist O et al. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. *Neuroreport* 12(4), 851–855 (2001).

Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, De La Monte SM. 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.* 8(3), 247–268 (2005).

Moloney AM, Griffin RJ, Timmons S, O’connor R, Ravid R, O’neill C. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer’s disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol. Aging* 31(2), 224–243 (2010).

Talbot K, Wang HY, Kazi H et al. Demonstrated brain insulin resistance in Alzheimer’s disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J. Clin. Invest.* 122(4), 1316–1338 (2012).

Dou JT, Chen M, Dufour F, Akkon DL, Zhao WQ. Insulin receptor signaling in long-term memory consolidation following spatial learning. *Learn. Mem.* 12(6), 646–655 (2005).

Moosavi M, Naghdil N, Maghsoudi N, Zahedi Ad S. The effect of intrahippocampal insulin microinjection on spatial learning and memory. *Horm. Behav.* 50(5), 748–752 (2006).

Stranahan AM, Norman ED, Lee K et al. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus* 18(11), 1085–1088 (2008).

Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nat. Neurosci.* 11(3), 309–317 (2008).

Pedersen WA, McMullan PJ, Kildstad JJ, Leverenz JB, Craft S, Haynatzki GR. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. *Exp. Neurol.* 199(2), 265–273 (2006).

Pintana H, Apajai N, Pratichyasakul W, Chattipakorn N, Chattipakorn SC. Effects of metformin on learning and memory behaviors and brain mitochondrial functions in high fat diet induced insulin resistant rats. *Life Sci.* 91(11–12), 409–414 (2012).

Ho L, Qin W, Pompl PN et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer’s disease. *FASEB J.* 18(7), 902–904 (2004).

Ramos-Rodriguez JJ, Ortis-Barajas O, Camero-Carrasco C et al. Prediabetes-induced vascular alterations exacerbate central pathology in APP23/PS1dE9 mice. *Psychoneuroendocrinology* 48 123–135 (2014).

Jimenez-Palomares M, Ramos-Rodriguez JJ, Lopez-Acosta JF et al. Increased Abeta production prompts the onset of glucose intolerance and insulin resistance. *Am. J. Physiol. Endocrinol. Metab.* 302(11), E1373–E1380 (2012).

Park S, Kim Da S, Kang S, Moon NR. β-amyloid-induced cognitive dysfunction impairs glucose homeostasis by increasing insulin resistance and decreasing beta-cell mass in non-diabetic and diabetic rats. *Metabolism* 62(12), 1749–1760 (2013).

Costello DA, Claret M, Al-Qassab H et al. Brain deletion of insulin receptor substrate 2 disrupts hippocampal synaptic plasticity and metastability. *PLoS ONE* 7(2), e31124 (2012).

Schechter R, Beju D, Miller KE. The effect of insulin deficiency on tau and neurofilament in the insulin knockout mouse. *Biochem. Biophys. Res. Commun.* 334(4), 979–986 (2005).

Schubert M, Gautam D, Surjo D et al. Role for neuronal insulin resistance in neurodegenerative diseases. *Proc. Natl Acad. Sci. USA* 101(9), 3100–3105 (2004).

De La Monte SM. Insulin resistance and Alzheimer’s disease. *BMB Rep.* 42(8), 475–481 (2009).

Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer’s disease: implications for treatment. *CNS Drugs* 17(1), 27–45 (2003).

De La Monte SM. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer’s disease. *Curr. Alzheimer Res.* 9(1), 35–66 (2012).

Watanabe T, Miyazaki A, Katagiri T, Yamamoto H, Idei T, Iguchi T. Relationship between serum insulin-like growth factor-1 levels and Alzheimer’s disease and vascular dementia. *J. Am. Geriatr. Soc.* 53(10), 1748–1753 (2005).

Sharma B, Singh N. Behavioral and biochemical investigations to explore pharmacological potential of PPAR-gamma agonists in vascular dementia of diabetic rats. *Pharmacol. Biochem. Behav.* 100(2), 320–329 (2011).

Bosco D, Plastino M, Cristiano D et al. Dementia is associated with insulin resistance in patients with Parkinson’s disease. *J. Neurol. Sci.* 315(1), 39–43 (2012).

Lalic NM, Marie J, Svetel M et al. Glucose homeostasis in Huntington disease: abnormalities in insulin sensitivity and early-phase insulin secretion. *Arch. Neurol.* 65(4), 476–480 (2008).

Craft S, Claxton A, Baker L et al. Therapeutic effects of long-acting intranasal insulin detemir for Alzheimer’s dementia or mild cognitive impairment. *Alzheimer’s Dementia* 9(4), P139–P140 (2013).

Freiher J, Hallschmid M, Frey WH et al. Intranasal insulin as a treatment for Alzheimer’s disease: a review of basic research and clinical evidence. *CNS Drugs* 27(7), 505–514 (2013).

Holscher C. First clinical data of the neuroprotective effects of PPAR-gamma agonists. *Am. J. Geriatr. Psychiatry* 13(11), 950–958 (2005).
Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. *Neurobiol. Aging* 32(9), 1626–1633 (2011).

Schintu N, Frau L, Ibba M *et al.* PPAR-gamma-mediated neuroprotection in a chronic mouse model of Parkinson’s disease. *Eur. J. Neurosci.* 29(5), 954–963 (2009).

Kiae M, Kipiani K, Chen J, Calingasan NY, Beal MF. Peroxisome proliferator-activated receptor-gamma agonist extends survival in transgenic mouse model of amyotrophic lateral sclerosis. *Exp. Neurol.* 191(2), 331–336 (2005).

Jin J, Albertz J, Guo Z *et al.* Neuroprotective effects of PPAR-gamma agonist rosiglitazone in N171–82Q mouse model of Huntington’s disease. *J. Neurochem.* 125(3), 410–419 (2013).

Gold M, Alderton C, Zsartau-Hind M *et al.* Rosiglitazone monotherapy in mild-to-moderate Alzheimer’s disease: results from a randomized, double-blind, placebo-controlled Phase III study. *Dement. Geriatr. Cogn. Disord.* 30(2), 131–146 (2010).

Harrington C, Sawchak S, Chiang C *et al.* Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer’s disease: two Phase 3 studies. *Curr. Alzheimer Res.* 8(5), 592–606 (2011).

Miller BW, Willett KC, Desilets AR. Rosiglitazone and pioglitazone for the treatment of Alzheimer’s disease. *Ann. Pharmacother.* 45(11), 1416–1424 (2011).

Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab.* 17(6), 819–837 (2013).

Lovshin JA, Drucker DJ. Incretin-based therapies for Type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* 5(5), 262–269 (2009).

Knauf C, Cani PD, Perrin C *et al.* Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. *J. Clin. Invest.* 115(12), 3554–3563 (2005).

During MJ, Cao L, Zussga DS *et al.* Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat. Med.* 9(9), 1173–1179 (2003).

Heile AM, Wallrapp C, Klinge PM *et al.* Cerebral transplantation of encapsulated mesenchymal stem cells improves cellular pathology after experimental traumatic brain injury. *Neurosci. Lett.* 463(3), 176–181 (2009).

Holscher C. The incretin hormones glucagon like peptide 1 and glucose-dependent insulinotropic polypeptide are neuroprotective in mouse models of Alzheimer’s disease. *Alzheimers Dement.* 10(Suppl. 1), S47–S54 (2014).

Perry TA, Greig NH. A new Alzheimer’s disease interventive strategy: GLP-1. *Curr. Drug Targets* 5(6), 565–571 (2004).

Bomfim TR, Forney-Geramo L, Sathler LB *et al.* An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer’s disease-associated Abeta oligomers. *J. Clin. Invest.* 122(4), 1339–1353 (2012).

Rachmany L, Tweedie D, Li Y *et al.* Exendin-4 induced glucagon-like peptide-1 receptor activation reverses behavioral impairments of mild traumatic brain injury in mice. *Age (Dordr.)* 35(5), 1621–1636 (2013).

Tweedie D, Rachmany L, Rubovitch V *et al.* Exendin-4, a glucagon-like peptide-1 receptor agonist prevents mTBI-induced changes in hippocampus gene expression and memory deficits in mice. *Exp. Neurol.* 239, 170–182 (2013).

Eakin K, Li Y, Chiang YH *et al.* Exendin-4 ameliorates traumatic brain injury-induced cognitive impairment in rats. *PLoS ONE* 8(12), e82016 (2013).

Egefjord L, Gejl M, Moller A *et al.* Effects of liraglutide on neurodegeneration, blood flow and cognition in Alzheimer’s disease – protocol for a controlled, randomized double-blinded trial. *Dan. Med. J.* 59(10), A4519 (2012).