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The nature, significance, and glucagon-like peptide-1 analog treatment of brain insulin resistance in Alzheimer's disease

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Abstract Alzheimer's disease (AD) is an age-related neurodegenerative disease leading over the course of decades to the most common form of dementia. Many of its pathologic features and cognitive deficits may be due in part to brain insulin resistance recently demonstrated in the insulin receptor→insulin receptor substrate-1 (IRS-1) signaling pathway. The proximal cause of such resistance in AD dementia and amnestic mild cognitive impairment (aMCI) appears to be serine inhibition of IRS-1, a phenomenon likely due to microglial release of inflammatory cytokines triggered by oligomeric Aβ. Studies on animal models of AD and on human brain tissue from MCI cases at high risk of AD dementia have shown that brain insulin resistance and many other pathologic features and symptoms of AD may be greatly reduced or even reversed by treatment with FDA-approved glucagon-like peptide-1 (GLP-1) analogs such as liraglutide (Victoza). These findings call attention to the need for further basic, translational, and clinical studies on GLP-1 analogs as promising AD therapeutics.

Keywords: Alzheimer's disease; Glucagon-like peptide-1; Inflammation; Insulin receptor; Insulin receptor substrate-1; Insulin signaling; Hippocampus; Liraglutide; Streptozotocin; Type 3 diabetes

1. Introduction

Until recently, Alzheimer's disease (AD) was considered synonymous with a type of neurodegenerative dementia associated with abnormally high densities of amyloid β (Aβ) plaques and neurofibrillary tangles in the forebrain. Today, however, AD is more broadly defined to include the underlying pathophysiologic processes that gradually lead to dementia [1,2]. Over the course of decades, AD pathology develops gradually in three phases [3,4]: (a) a preclinical period beginning with asymptomatic accumulation of Aβ leading to early neurodegeneration and then to subtle cognitive symptoms [2,5]; (b) a prodromal period known as mild cognitive impairment (MCI) due to AD in which the first clear, but not incapacitating, clinical symptoms emerge [6,7]; and (c) dementia due to AD [4,8] This final phase of the disorder commonly manifests at ≥65 years of age, but can emerge as early as age 30 years in relatively rare familial cases [3]. The personal impact of this last phase is devastating, ultimately robbing its victims of their identity, their capacity to care for themselves, and their ability to recognize or communicate with others.

AD dementia, the most common of all neurodegenerative dementias, is of special concern to society as a whole because it poses a clear public health risk of epidemic proportions worldwide [9] and because we lack effective treatments for it. Although >100 pharmacologic treatments for AD have been proposed and tested, most seeking to reduce brain levels of Aβ, none has proven more than minimally effective [10] for more than about a year after diagnosis [11]. If this situation persists, it is expected that at least

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13.8 million Americans will be afflicted with AD dementia by the year 2050, with healthcare costs for them costing $1.2 trillion [3].

There is consequently an urgent need for development of novel treatments of AD within the next decade [12]. Among the most promising of those now in development target brain insulin resistance (i.e., reduced neuronal responsiveness to extracellular insulin), which is an early, common, and major feature in AD cases with and without diabetes [13,14]. After outlining the history of research behind the discovery of brain insulin resistance, we discuss its nature, significance, probable cause, and promising treatments with GLP-1 analogs.

2. Discovery of brain insulin resistance in AD

Brain insulin resistance in AD was first proposed nearly 20 years ago by Siegfried Hoyer and colleagues [15,16], who hypothesized that desensitization of neuronal insulin receptors (IRs) may explain reduced brain glucose metabolism in this disorder. Although some [14,17], but not all [18], studies reported decreased IR sensitivity in the neocortex and/or hippocampus of AD cases, its relationship to reduced brain glucose metabolism in such cases remains uncertain, because it has been established that insulin by itself has no effect on neuronal glucose uptake in the forebrain [14,19] and also because Hoyer and coworkers relied on intracerebroventricular (ICV) streptozotocin (STZ) in rodents to test their hypothesis.

Since ICV STZ is often used to create animal models of brain insulin resistance [20] and AD [21], it must be explained why this drug treatment was insufficient to test the plausibility of brain insulin resistance in AD. The few studies that have directly tested the effect of STZ on insulin responsiveness were not conducted on the brain, but instead upon liver and muscle tissue after peripheral administration of the drug in rodents. The results of the these studies were inconsistent, showing that STZ either increases [22], does not affect [23], or decreases [24,25] insulin responsiveness in the tissues tested. The studies used to justify using ICV STZ to model brain insulin resistance were naturally those reporting STZ-induced inhibition of insulin responsiveness [24,25], but the mechanism for this claimed effect does not apply to the brain, as indicated in the following considerations. The depressive effect on insulin responsiveness is not produced by direct action on liver or muscle, but by the drug's rapid reduction of plasma insulin given that normal insulin responsiveness in STZ-treated animals can be restored by simply raising plasma insulin [24,25]. The ability of STZ, a glucose analog, to lower plasma insulin depends on its cellular uptake by glucose transporter 2 (GLUT2), which binds the glucose moiety of STZ [26]. Such uptake occurs preferentially in insulin-secreting pancreatic β cells, because they are among the few cell types in the rodent rich in GLUT2. Once taken up by the β cells, the *N*-methyl-*N*-nitrosurea moiety of STZ exerts its cytotoxic effects leading to cell death, and thus loss of pancreatic insulin secretion [26]. In the brain, however, GLUT2 is expressed at relatively low levels by few, if any, neurons expressing insulin, especially pyramidal neurons of the neocortex and hippocampus (CA1-3) [27–29]. This may explain why ICV STZ has not been shown to affect protein levels of brain insulin [30] and why this drug treatment has inconsistent effects on gene and/or protein expression of upstream versus downstream insulin signaling molecules within and across brain structures [31–33].

At present, then, there is no reason to expect (and no clear demonstration) that ICV STZ preferentially targets insulin signaling in the brain and, consequently, no reason to expect that it preferentially models brain insulin resistance. It is more likely that ICV STZ affects brain insulin signaling along with many other brain processes simply by inducing oxidative stress, glial inflammatory responses [33–35], and toxic effects on GLUT2 cells in the brain, including those in the hypothalamus and brainstem regulating autonomic control of pancreatic insulin and glucagon release, which disrupts systems ensuring sufficient glucose flux to the brain [36].

Pursuing evidence that brain insulin signaling was actually reduced in AD, Hoyer's group initiated study of insulin signaling molecules in postmortem cases of this disorder. As reported in 1998 by Frölich et al. [18], Hoyer's group found that normal humans exhibit significant reductions with age in neocortical levels of insulin and in insulin binding of neocortical IRs, but that AD cases were not significantly different in these respects from controls of similar age [18]. In 2005, Suzanne de la Monte and colleagues reported that gene and (less quantitatively assessed) protein expression of insulin and IR, as well as other insulin signaling molecules and IR insulin binding, were markedly lower in forebrains of AD cases compared to controls of unstated age [17,37]. Additional postmortem studies by other groups between 2005 and 2011 established that protein levels of insulin-signaling molecules do occur in AD cases when compared with age-matched controls [38–41]. The postmortem studies reported by 2011 nevertheless disagreed in many respects on the specific signaling molecules affected and whether the affected molecules were decreased or increased in AD [13,17,37–39].

By 2011, however, one consistent feature of AD brains had been identified, namely high serine phosphorylation of insulin receptor substrate-1 (IRS-1 pS) discovered by our group in the hippocampus [39] and confirmed there and in temporal neocortex by others [40,41]. Such phosphorylation inhibits IRS-1 and its ability to transmit IR signals to more downstream molecules [42]. Because elevated IRS-1 pS in adipose and muscle tissue is often associated with insulin resistance in type 2 diabetes (T2D) [42,43], we considered it plausible that T2D-induced IRS-1 pS elevation in the brain may help explain why T2D is a risk factor for AD [44]. We also considered