RESEARCH HIGHLIGHT

The Role of Insulin and Incretins in Neuroinflammation and Neurodegeneration

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Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP) are incretin hormones secreted from intestinal cells in response to incoming nutrients. The release of these incretins triggers the production and secretion of insulin from pancreatic β cells, which upregulates the transport of glucose from the blood stream into the muscles, liver and adipose tissue for storage; therefore, insulin and incretins are vital to maintaining energy homeostasis within the body. Recently, it has been recognized that the activity of these hormones is not limited to the periphery, but extends to the central nervous system (CNS) as well. Within the CNS, insulin and incretins function as components of the anti-apoptotic and growth-regulating signaling cascades. Moreover, anti-inflammatory and neuroprotective roles for these hormones in the CNS have also been demonstrated. Specific discoveries have been made suggesting that insulin, GLP-1 and GIP may inhibit pathological processes in several CNS diseases, such as Alzheimer's disease, Parkinson's disease, and schizophrenia.

Keywords: Alzheimer's disease; GIP; GLP-1; insulin; neurodegeneration; neuroinflammation; neuroprotection; Parkinson's disease; schizophrenia; type 2 diabetes

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Introduction

Following feeding, the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are secreted into the blood stream. These hormones travel to the pancreas, where they trigger the production and secretion of insulin. Insulin normalizes rising blood glucose levels by signaling to the liver, muscle and adipose cells to take up glucose and store it as glycogen, making insulin and incretins vital to the maintenance of energy homeostasis within the body [1-3]. In addition to their metabolic roles, insulin, GLP-1 and GIP have all shown to behave as inflammatory signaling molecules in the peripheral tissues [4-6]. Insulin negatively regulates nuclear factor kappa B (NFκB) in monocytes, thereby exhibiting its anti-inflammatory actions [7]. NFκB is a pro-inflammatory transcription factor, that initiates production of pro-inflammatory cytokines and upregulates enzymes that generate reactive oxygen species (ROS) [7,8]. Other reports state a more complex role for insulin in inflammatory processes, showing that insulin exhibits short-term anti-inflammatory (decreased NFκB transcriptional activity) effects and long-term pro-inflammatory (enhanced NFκB transcriptional activity) effects in hepatocytes [4].

Incretins also have demonstrated roles in the peripheral inflammation. GIP acts as a pro-inflammatory mediator by inducing the secretion of interleukin (IL)-6 and IL-1β from adipose tissue [5], while GLP-1 reduces macrophage infiltration into adipose tissue in obese mice and directly

inhibits production of IL-6, tumor necrosis factor (TNF)-α and monocyte chemoattractant protein 1 from adipocytes [6].

Insulin and incretins are capable of crossing the blood brain barrier (BBB), and exerting their actions not only on neurons, but also on the non-neuronal glial cells, which include microglia, astrocytes and oligodendrocytes. Microglia are the resident macrophages of the central nervous system (CNS), which specialize in phagocytosis and antigen presentation [9]. Astrocytes are involved in brain repair and support of neurons [10]. Oligodendrocytes insulate neuronal processes and also support the neurons [11]. In response to an infection or injury, brain glia become activated and release inflammatory mediators to protect against the harmful stimuli.

Insulin crosses the BBB via an active transport mechanism and plays important metabolic and homeostatic roles in the CNS, including promotion of cellular growth and differentiation, enhancement of memory formation and activation of glycogen synthesis [12,13]. Our data indicate that, within the CNS, insulin may play a pro-inflammatory role at low concentrations and possess anti-inflammatory activity at higher concentrations (Spielman and Klegeris, unpublished observations).

It has been demonstrated that incretin molecules cross the BBB by simple diffusion. In the brain, GLP-1 promotes neuronal growth and proliferation; induces neurite outgrowth; and inhibits neuronal apoptosis [14]. Whereas GIP derivatives have been shown to decrease microglia activation in mice[15]. This evidence makes it clear that insulin and incretin molecules are likely important inflammatory signaling molecules in the CNS, which demonstrate specific actions both on neurons and glial cells. This research highlight will focus on recent evidence of the neuroimmunoregulatory and CNS pathology-modifying potential of insulin and two of the incretins, GLP-1 and GIP.

Regulation of Neuroinflammation by Insulin

In the CNS, insulin activates the phosphatidylinositol 3-kinase (PI3K)-dependent pathway and mitogen-activated protein kinase (MAPK) pathways [16, 17]. In addition to promoting cell survival and increasing synaptic signaling [18, 19], activation of the PI3K pathway leads to phosphorylation of IkappaB kinase α (IKKα), which activates the NFκB pathway and leads to the transcription of apoptosis regulators, cytokines, chemokines and growth factors [20, 21]. Activation of the MAPK pathways, on the other hand, leads to cellular growth and survival [22, 23], as well as transcription of pro-inflammatory cytokines [24], and production of superoxide radicals by nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidase [25]. Insulin in the CNS appears to have somewhat paradoxical effects by exhibiting both neuroprotective and pro-inflammatory properties. However, the precise role of insulin in modulation of CNS inflammation is only emerging, and cannot be proclaimed yet as strictly detrimental or protective. For example, insulin inhibited expression of inducible nitric oxide synthase (iNOS), as well as hydrogen peroxide-induced damage in rat astrocytes, which had been stimulated with lipopolysaccharide (LPS) [26, 27]. Moreover, rodent astrocyte cell culture studies with streptozotocin (STZ)-induced insulin resistance exhibited increased activation, as indicated by increased expression of glial fibrillary acidic protein (GFAP); upregulated markers of inflammation, as indicated by the increased translocation of NFκB into the nucleus; and elevated secretion of the pro-inflammatory cytokines TNF-α and IL-1β [28]. However, pretreatment of astrocytes with insulin prior to administration of STZ reduced or obliterated all of the above abnormalities.

Downstream activation of protein kinase B (Akt) and NFκB by insulin induces a negative feedback loop involving toll-like receptor signaling, thereby reducing inflammation in the CNS [29]. Insulin also has anti-inflammatory properties during CNS sepsis by inhibiting the production of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α, and by alleviating oxidative stress, as evident by decreased levels of malondialdehyde and hydrogen peroxide in the brains of septic rats [30]. Furthermore, diabetic rats showed significant increases in gliosis (expression of GFAP and major histocompatibility complex (MHC) II markers), compared to non-diabetic rats and diabetic rats, which had received insulin treatment, thereby indicating that the lack of circulating insulin impacts the CNS in a pro-inflammatory manner [31]. Similar to many other hormones [32-34], insulin may provide beneficial effects within a particular physiological concentration range, however lack of insulin [30, 31] as well as excess insulin seem to exhibit detrimental pro-inflammatory effects in the CNS [35].

The Role of Insulin in Neurodegenerative Diseases

Insulin has long been recognized as a hormone, which serves specific neuroprotective functions in the CNS. Insulin promotes cell survival by inhibiting apoptosis-inducing peptides and by enhancing neurite outgrowth and synapse formation, which facilitates neuronal growth and differentiation. Insulin also facilitates learning and memory through its positive effects on synaptic function [12, 13, 36, 37]. Studies have shown that insulin promotes normal functioning of CNS mitochondria, and that absence of insulin causes depolarization of mitochondria, leading to the generation of excess ROS, thus demonstrating possible neuroprotective roles for insulin in the CNS [38].

Insulin resistance and related insulin dysfunction has been pin-pointed in the pathogenesis of several neurodegenerative

Table 1. Insulin dysfunction in select CNS pathologies

Disease	Insulin Related Pathology
Alzheimer's disease	- Decreased CNS insulin concentrations [86] - Decreased insulin signaling cascade activation [87] - Decreased insulin leads to an increase in neurofibrillary tangles and amyloid beta plaques [88], the hallmarks of AD.
Parkinson's disease	- Decreased CNS insulin concentrations [86] may contribute to increased deposition of α-synuclein [89], which make up PD Lewy bodies.
Huntington's disease	- Reduced level of Akt, the molecule central to the insulin signaling pathway[86].
Major depressive disorder	- Decreased CNS insulin concentration [90]. - Insulin positively regulates dopamine neurotransmission [47, 91] and synaptic clearance of dopamine [92], which is the major neurotransmitter associated with feelings of happiness.
Schizophrenia	- Higher circulating insulin levels compared to healthy controls, which correlates with insulin resistance [86, 93].

pathologies including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, major depressive disorder (MDD) and schizophrenia (see Table 1 and a review by Spielman *et al.,* 2014 [39]).

Insulin therapies are being tested as a potential treatment in several neurodegenerative disorders based on the following observations: (1) insulin dysfunction in several CNS diseases (Table 1); (2) the observed potential of insulin to alleviate cytotoxic insult to neuronal cells in culture [40]; (3) its ability to enhance learning and memory in rodents [41, 42]. For example, the administration of intranasal insulin has already shown promising effects in humans by halting further memory loss in mild cognitive impairment and Alzheimer's disease [43, 44]. These studies found that intranasal insulin acutely improved memory in AD patients, even after a single administration of insulin [45]. Insulin treatment also increased levels of plasma Aβ; it has been shown that AD patients typically have lower plasma Aβ compared to healthy controls, although mixed results have been reported [45,46].

Rodent studies have demonstrated that insulin is required for normal release and clearance of dopamine, and absence of insulin nearly obliterates dopamine release all together (approximately 75% reduction) [47]. The insulin sensitizers, pioglitazone and rosiglitazone, have been used in clinical trials for treatment of MDD, and have shown to decrease the severity of symptoms of depression by up to 39% according to the Hamilton Depression Rating Scale [48,49].

Use of insulin in neurological diseases is not completely novel. In the early 1900s, insulin-induced comas were utilized as an effective treatment option for schizophrenia[50]. This particular method of schizophrenia treatment decreased in popularity, only after the discovery of new superior drug treatments. It was phased out of the clinical practice primarily due to the intensive physician and nursing staff supervision required during this procedure [51].

Recent studies have also highlighted the role that insulin-enhancing incretin hormones may play in neuroinflammation and neuronal health. These data indicate the potential for a combined administration of insulin and incretins in the treatment of neurological disorders.

Regulation of Neuroinflammation by Incretins

The two main incretin hormones, GIP and GLP-1 are secreted from K cells [52] and L cells [53] of the small intestine respectively, and primarily function to stimulate insulin secretion from the pancreas. In addition to stimulation of insulin release and inhibiting apoptosis of pancreatic β cells, incretins stimulate fat accumulation in adipose tissue, and promote memory formation in the CNS [54, 55]. Research shows that GIP and GLP-1 also play inflammatory roles in both the periphery and the CNS.

Passage of GLP-1 and GIP across the BBB occurs by simple diffusion [56, 57]. The GIP receptor (GIPR) has been detected on neuronal cells, but is yet to be detected on microglia or astrocytes [58, 59]. GLP-1 receptors (GLP-1R), on the other hand, are located on neurons [60], astrocytes [61] and microglia [61] in mice, but in humans have only been confirmed in neurons [62]. These findings indicate that both GLP-1 and GIP may exhibit immunomodulatory functions in the CNS, however the investigation of such function of incretins in the CNS is very novel and only a few specific discoveries have been made to date.

Within the CNS, GLP-1 has been shown to reduce the secretion of IL-1β from activated rat microglia and astrocytes [61]. Additional rodent studies have shown that the longer-lasting GLP-1 analogue exendin-4 decreases oxidative stress and glial cell activation following events of cerebral ischemia [63]. A second GLP-1 mimetic, liraglutide, displays anti-inflammatory properties in mice with intracerebral hemorrhage by reducing the number of CNS infiltrating neutrophils [64]. Liraglutide also reduces microglia activation in the brains of AD mouse models; thereby indicating possible anti-inflammatory actions of GLP-1 within the CNS during pathological conditions [65].

The inflammatory effects of GIP in the CNS are less studied. However in the periphery, GIP acts as a

pro-inflammatory mediator and induces the secretion of IL-6 and IL-1β from adipose tissue [5]. Infusions of GIPR agonists in apolipoprotein E deficient (apoE$^{-/-}$) mice inhibited monocyte/macrophage infiltration into aortic walls [66]; thus, GIP may inhibit monocyte/macrophage infiltration into the CNS in a similar fashion. Studies have also demonstrated that the acetylated GIP analogue, D-Ala^{2}GIP, reduces activation of microglia [15] and astrocytes [67] in AβPP/PS1 AD mice (transgenic mouse model of AD with rapid Aβ deposition), thereby decreasing subsequent neuroinflammation.

Incretins in the Treatment of Neurodegenerative Diseases

In addition to their inflammatory roles, much like insulin, GIP and GLP-1 are neuroprotective. GLP-1 promotes neuronal growth and proliferation; induces neurite outgrowth; facilitates synaptic transmission; and inhibits neuronal apoptosis [14, 68-70]. The recently discovered anti-inflammatory and neuroprotective properties of these hormones have sparked novel research into their potential roles as modulators of neuroinflammatory and neurodegenerative diseases.

Since GLP-1 and GIP enhance insulin signaling, the synthetic incretins (such as liraglutide and lixisenatide) and also incretin-degrading enzyme dipeptidyl peptidase-IV (DPP-IV) inhibitors (such as sitagliptin) have been used as treatment options for type 2 diabetes patients [71-73]. More recently these drugs have been investigated and implemented in clinical studies for treatment of certain neurodegenerative disorders exhibiting central insulin resistance, such as AD and PD [69, 74].

GLP-1 has been shown to enhance the long-term potentiation (LTP) in rats, and reverse the LTP impairments associated with Aβ deposition in AD [70]. A recent study showed that intraperitoneal injections of the synthetic GLP-1 drug liraglutide in AβPP/PS1 mice reduced Aβ plaque load approximately two fold in this AD rodent model [75]. This study showed that in addition to improving the AD pathology on a cellular level, the AD symptoms of memory loss and learning deficits also improved with the administration of liraglutide [65, 75]. Liraglutide is currently being tested in clinical trials involving AD patients [76].

Exendin-4, a degradation-resistant GLP-1 analogue, has been shown to protect primary cortical and dopaminergic neurons exposed to the PD inducing toxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) both in rodent and human cell cultures [77]. Clinical trials investigating the efficacy of exendin-4 (exenatide) in the treatment of PD have shown promising results [78]. Phase two clinical trials demonstrate improvement in motor skills and cognition of PD patients given subcutaneous exenatide injections [79].

Both liraglutide and exenatide have also shown potential for the treatment of psychiatric and mood disorders. A study using a mouse model of apomorphine-induced psychosis showed that liraglutide reduced psychosis-related behavior in mice more than two fold when compared to the control group [74]. Intraperitoneal injections of exenatide reduced anxiety-like behavior in mice by approximately 50% and reduced depressive behavior by approximately 10% [80]. The success of GLP-1R agonists in alleviating symptoms of psychosis and depression in mice models has led to a clinical trial [81], which is currently testing the efficacy and safety of exenatide in the treatment of weight gain and in the clinical improvements of emotional and mental symptoms in patients with mania, MDD and schizophrenia [82].

In addition to the study of GLP-1 in the treatment of neurodegenerative disorders, GIP has also been highlighted in a recent study aimed at alleviating pathologies and symptoms associated with AD. GIP derivatives have been shown to decrease microglia activation in a mouse model of AD [15], and also reverse Aβ-induced impairment in LTP of synaptic transmission in mice [83]. Two recent studies by Faivre and Holscher highlighted the potential of D-Ala^{2}GIP in the treatment of AD pathologies and symptoms. Chronic intraperitoneal administration of D-Ala^{2}GIP in AβPP/PS1 mice showed a reduction in plaque load by approximately 30%, and a decrease in Aβ-associated inflammation and microglia activation by approximately 20% [15, 84] making this GIP analogue a potential candidate for the treatment of AD in humans.

Conclusion

Research driven by the observations that insulin, GLP-1 and GIP can cross the BBB and bind their respective receptors in the CNS has led to the fascinating discovery of the anti-inflammatory and neuroprotective properties of these hormones. This discovery has prompted investigations into the neurodegenerative disease-combating potential of insulin and incretins. Since insulin/GLP-1 combinations have shown improved effectiveness in the treatment of peripheral endothelial dysfunction [85], perhaps combinations of these and similar hormones in a drug treatment cocktail could be optimized as the treatment strategies for diseases like AD, PD, MDD and schizophrenia. Future studies on the pathology-reducing potential of these hormones are essential. In-depth studies of the anti-inflammatory and neuroprotective properties of insulin, GLP-1 and GIP will provide fundamental knowledge on the role of these hormones in the CNS, which could potentially be translated into effective CNS drugs and disease-modifying therapeutic strategies.

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Conflict of Interest

The authors declare that they have no conflicting interests.

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