Exenatide promotes the autophagic function in the diabetic hippocampus: a review

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ABSTRACT
The hippocampus is a vulnerable structure that can be affected by many damaging stimuli, contributing to the development of diabetic cognitive dysfunction. One of these stimuli is autophagic dysregulation. Although autophagy is a physiological process that occurs at a basal level and is considered a pro-survival mechanism, autophagic dysregulation can turn it to be a pro-death mechanism, causing hippocampal neuronal loss. Exenatide is an anti-diabetic drug that has a neuroprotective role and is reported to improve diabetic cognitive deficits. It enhances glucose-dependent insulin secretion and acts via several mechanisms, including autophagy promotion through different pathways such as the brain protein kinase A signaling pathway. This review addresses the available data about the mechanisms responsible for the autophagic dysfunction in diabetic cases, and the enhancing effect of exenatide on autophagic function. More investigations are required to elucidate the consequences of the over-stimulation, impairment, or late-stage inhibition of autophagy, and the molecular mechanisms underlying the promoting action of exenatide on the autophagic process in the diabetic hippocampus.

Introduction
Diabetes mellitus (DM) can affect the neuroanatomical, neurophysiological, and neurochemical functions of the brain, resulting in cognitive deficits in memory, learning, attention, psychomotor speed, or executive function [1]. The hippocampus is regarded as a vulnerable structure in the brain that can be damaged by a variety of stimuli, causing many cognitive deficits [2].

Among the mechanisms known to participate in diabetic brain affection is autophagy, as autophagic dysregulation can correlate with the proinflammatory signaling via the oxidative stress pathway, and may take part in the development of insulin resistance as well [3]. Furthermore, the inhibition of autophagy may lead to the impairment of insulin secretion [4].

Exenatide is an anti-diabetic drug that acts as a glucagon-like peptide-1 (GLP1) agonist. It is a synthetic 39-amino-acid peptide amide that has the same amino-acid sequence of exendin 4 ‘an isolated peptide from lizard saliva’, and shares 53% of its amino acid sequence with human GLP-1 [5]. It enhances glucose-dependent insulin secretion [6], and is suggested to have a neuroprotective role [7].

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Exenatide is reported to enhance autophagy, and reduce apoptosis in a rat model of doxorubicin-induced cardiotoxicity [8]. Besides, it induced autophagy and prevented cell regrowth in the human hepatocellular carcinoma HepG2 cell line [9]. Also, it improved the hippocampal autophagic activity in a rodent model of Alzheimer’s disease [10]. Although some case reports stated that exenatide induced pancreatitis through the impairment of the autophagic flux [11], another study reported that exenatide not only did not induce pancreatitis but also relieved chemically-induced pancreatitis in normal and diabetic rats [12].

This review addresses the role played by autophagy in the pathogenesis of diabetic hippocampal affection, and the molecular mechanisms that explain the enhancement of the autophagic function associated with the exenatide administration.

**Methodology**

We searched the online databases (PubMed, Scopus, and Web of Science) using the advanced search strategies, to search for the following vocabulary (diabetes or diabetic, hippocampus or cognitive, exenatide or exendin-4, and autophagy). The search results were evaluated for the latest updates regarding the autophagic process in the diabetic hippocampus, and the effect of exenatide on modifying this process.

**Main text**

*Diabetic cognitive dysfunctions*

Diabetic cognitive dysfunctions can arise from several contributing factors that vary between metabolic, vascular, endocrinal, and brain-related factors. Metabolic factors include chronic hyperglycemia, recurrent hypoglycemia, and protein glycation. Vascular complications range between microvascular disease as diabetic retinopathy, macrovascular disease as cardiovascular affection, and endothelial dysfunction. Endocrinal factors comprise reduced insulin sensitivity, hyperinsulinemia, and hyperleptinaemia. Brain-related factors may include amyloid disposition, oxidative stress, changes in neuronal calcium homeostasis, and genetic predisposition [1]. Though the incidence rate of diabetic cognitive dysfunction is increased with aging, it can occur throughout diabetes, even in patients with impaired fasting glucose [13].

The hippocampus is one of the brain regions that is extensively studied in multiple neurological and neuropsychiatric disorders, because of its vulnerability to damage, being a readily identifiable structure both grossly and microscopically, and playing an important role in many cognitive functions such as learning and memory [14]. In addition, the hippocampus is one of the unique areas in the brain where little neurogenesis continues in adult life, however, hippocampal atrophy represents a more attractive drug target, as it can result from deposition of beta-amyloid, suppression of neurogenesis, impairment of long-term potentiation, oxidative stress, metabolic stress, and other mechanisms [2].

*Molecular mechanisms of autophagy*

The degradation of cellular components can be achieved by two major systems: the ubiquitin-proteasome system and autophagy. The ubiquitin-proteasome system is concerned with the degradation of the short-lived proteins, as they are tagged by ubiquitin, and recognized and degraded by the proteasome. Autophagy is the process by which eukaryotic cells get rid of intracellular organelles and protein aggregates that cannot be degraded by the proteasome. It degrades long-lived proteins, lipids, and cytoplasmic organelles via a lysosome-driven process [15, 16]. It occurs at a basal level in all cells, and it helps maintain cellular homeostasis. Also, it is proven to have a role in development and disease [17].
Autophagy has three different types: chaperone-mediated autophagy which deals with the unfolded soluble proteins, microautophagy which deals with the cytosolic components by invagination, and macroautophagy which deals with the cytoplasmic cargo by the ordered process of autophagy [18].

The autophagic process comprises four steps: initiation, nucleation, the fusion of autophagosome and lysosome, and hydrolyzation. Nucleation is the first morphological step, in which the phagophore—an isolation membrane—is formed. Then, the elongation of the phagophore and fusion of its edges leads to the formation of a double-membrane structure holding cytoplasmic content, named the autophagosome. The autolysosome is formed by the fusion between the outer membrane of the autophagosome and a lysosome. The final step is the hydrolyzation of the inner membrane of the autophagosome and the engulfed cytoplasmic content (Figure 1) [19].

Lysosomes are the main organelles regulating all the steps following autophagosome formation. They are capable of breaking down any biological material, as they contain acid hydrolases. Their integrity is primarily influenced by two factors: the soluble acid hydrolases and the lysosomal membrane proteins. A vacuolar ATPase maintains an acidic (pH ≤5) milieu by pumping protons into the lysosomal lumen, making the acid hydrolases able to work. The lysosomal membrane proteins such as lysosome-associated membrane protein (LAMP-1 & LAMP-2) act to protect the cytoplasm from the action of the acid hydrolases and regulate the fusion of the lysosomes with other organelles, including the autophagosomes [15].

![Figure 1. Schematic illustration of the steps of autophagy. The phagophore assembly site (PAS) denotes the proposed site for autophagosome formation, to which most of the core autophagy-related proteins (ATG) are recruited. The elongation of the phagophore forms the autophagosome, which undergoes maturation by fusion with a lysosome. Finally, the autophagosome inner membrane and cargo are degraded, with the recycling of the resultant macromolecules. Many regulatory components control the steps of autophagy such as the vesicle membrane protein (VMP1) that can trigger autophagy by its overexpression and might function as a transmembrane protein, the UNC-51-like kinase (ULK) complex that contains various ATG proteins, the class III phosphatidylinositol 3-kinase (PtdIns3K) complex that is involved in autophagosome formation or clearance, the lipidated form of LC3 (LC3-II) that is attached to both faces of the phagophore, and TP53INP2 that can interact with LC3 as well as VMP1 [20].](image-url)
**Autophagic markers**

Autophagy is a dynamic process, and the autophagic flux refers to the rate of turnover of autophagic vacuoles implying the whole process of autophagy [21]. Microtubule-associated protein Light Chain 3 (LC3) is an essential contributor to the conjugation system for autophagosome formation. Although it is present in the nucleus and cytoplasm, it functions mainly in the cytoplasm [22]. LC3-I represents its immature form, which is further activated by lipidation to LC3-II, in the presence of Atg7 and Atg5. LC3-II is regarded as a marker of autophagy formation, as it is associated with the outer and inner membranes of the autophagosome [23, 24].

Usually, an increase in the rate of autophagy is followed by an increase in LC3-II, but it is not the rule for all cases. The activation of LC3-I to LC3-II by lipidation can occur even if the autophagosome formation is blocked, and LC3-II can accumulate even if there is a late-stage inhibition of the autophagy because it is degraded in the autolysosome. Therefore, the increased LC3-II level can be an indicator of autophagy stimulation or late-stage inhibition due to blockage of the downstream steps in autophagy [24].

Another marker of autophagy is p62, which is located on chromosome 5 and expressed in all tissues. It is an adaptor protein with an LC3-interacting region; thus, it undergoes degradation with LC3 present in the inner membrane of the autophagosome. It has a role in nucleation induction of the autophagosome membrane, followed by recruitment of ubiquitylated proteins and degradation through autophagy [17, 25, 26]. Consequently, autophagy activation is accompanied by a decrease in the p62 level [19]. To sum up, autophagy activation can be detected by analysis of LC3 and p62 in tandem, where it is anticipated to have an increased ratio of LC3-II to LC3-I and a reduction in p62 protein level [27].

**Autophagy under cellular stress**

Under cellular stress, autophagy allows active rearrangement of nutrients from unnecessary processes to more vital processes, which is critical for cell survival [28]. This autophagic response is principally integrated through the mammalian target of rapamycin complex 1 (mTORC1), which is activated under normal conditions, causing a negative regulation of the autophagy initiation. Conversely, under stressful conditions such as starvation or energy depletion, various upstream regulators function to inhibit the mTORC1 and activate the autophagy machinery [27].

Typically, β-cells are subjected to a high protein burden, because of the synthesis of the proinsulin at a rate of 106 molecules/min, which makes them highly susceptible to endoplasmic reticulum (ER) stress due to the accumulation of misfolded protein. The protecting role of autophagy on β-cells was confirmed when the Atg7 knock-out mice exhibited islet degeneration, glucose intolerance, and impaired insulin secretion [29]. Factors such as chronic low-grade inflammation, glucotoxicity, lipotoxicity, and islet amyloid polypeptide (IAPP) can induce the accumulation of misfolded proinsulin and the mTORC1 activation, which lead to ER stress. If the ER stress exceeds the ER functional capacity, the death of β-cell can occur by apoptosis. However, the mTORC1 inhibitors such as rapamycin and the misfolded protein itself can activate autophagy, stopping the ER stress-induced β-cell apoptosis (Figure 2) [30].

Additionally, the autophagic impairment may contribute to the development of insulin resistance, as the accumulation of dysfunctional mitochondria results in elevated levels of reactive oxygen species (ROS) that overwhelm the cytoprotective capacity of autophagy, which is implicated as one of the mechanisms of insulin resistance [31]. Insulin resistance can develop in the neural tissue as well. Indeed, the neural tissue is insulin-independent for containing
the glucose transporters GLUT1 and GLUT3, but it is insulin-responsive, as insulin receptors are widely expressed in the brain [3].

**Autophagy in diabetes mellitus**

The observations of autophagic activity in diabetic cases show quite a variability; this could be explained by understanding that these changes represent the net effect of various factors that differ following the type and pathophysiology of DM, and the metabolic alteration that predominates. For instance, insulin is known to inhibit autophagy by phosphorylation, so deficient insulin promotes autophagy. However, insulin resistance induces the accumulation of autophagosomes [32]. Moreover, hyperglycemia suppresses autophagy by decreasing the formation of autophagosomes and autolysosomes (Figure 3) [33]. Autophagy is a pro-survival process, even though, the excessive degradation of cellular constituents may convert it into a pro-death mechanism [34].

**Autophagy in the diabetic hippocampus**

The diabetic hippocampus can display activated autophagy, evidenced by increased levels of ATG5, ATG7, and LC3 II, and decreased levels of p62, which allows autophagy to play a neuroprotective role against diabetic cognitive dysfunction [35]. In other studies, autophagy exhibited an activation with late-stage inhibition, evidenced by increased levels of beclin-1 - a key molecule involved in the formation of the autophagosome and sorting of lysosomal proteins- and LC3 II, and decreased levels of LAMP1 and LAMP2, as markers of lysosomal function [19], and evidenced by the increased level of LC3II, and increased level of p62 [36]. [37], reported that DM is associated with impairment of autophagic flux due to lysosomal dysfunction. While in other studies, hyperglycemia was associated with impaired autophagy, evidenced by decreased level of LC3II, and an increased level of p62 [33].

![Figure 2](image-url) **Figure 2.** The relation between ER stress, apoptosis & autophagy. Many diabetic factors including hyperglycemia and oxidative stress can lead to increased proinsulin misfolding and mTORC1 activation, with subsequently inhibited autophagy and ER stress, and ultimately β-cell death via apoptosis. The mTORC1 inhibitors such as rapamycin can activate autophagy, stopping the ER stress and β-cell apoptosis. Eventually, these events lead to decreased proinsulin and insulin biosynthesis. Protein kinase R (PKR)-like eukaryotic inhibition factor 2a kinase (PERK), inositol requiring enzyme 1alpha (IRE1α), activating transcription factor 6 (ATF6) [30].
Effects of exenatide as an anti-diabetic drug

Exenatide is a synthetic anti-diabetic drug that modulates insulin release by enhancing glucose-dependent insulin secretion. It acts as a GLP-1 agonist, which is an incretin hormone, whose receptors are largely expressed throughout the body including the hippocampus. Exogenous GLP-1 administration is believed to restore blood glucose to near-normal levels, as diabetes is associated with the inactivation of the incretin system, which is thought to participate in the reduced regulation of insulin and glucagon secretion [6, 38].
Generally, exenatide is well tolerated by type-2 diabetic patients, even in diabetic patients suffering from heart failure [39]. Although it has a drawback that it is administered in a subcutaneous injection form that necessitates daily injections because of its short action time, this could be overcome by the combination with other anti-diabetic drugs using the once-weekly injection regimen [40], or the administration of the more recent GLP-1 agonist (semaglutide), which can be injected once weekly, or can be administered orally by co-formulating it with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate [41].

Exenatide exerts other important effects such as it protects β-cells against apoptosis, delays gastric emptying, reduces food intake, lowers body weight with low risk of hypoglycemia, decreases serum glucagon concentrations during periods of hyperglycemia, and is resistant to degradation by dipeptidyl peptidase IV [7, & 5]. Additionally, it has an anorectic effect that can impact the gut-brain axis in both normal and pathological conditions. The GLP-1 receptors are expressed in the nucleus tractus solitarius and the hypothalamus, affecting the appetite. Also, it is reported to have growth factor-like properties [38, 42].

**Figure 4.** A diagram demonstrating the mechanisms responsible for the effects of chronic continuous peripheral exenatide administration on type 2 diabetic rats. Exenatide may initiate an insulinotropic response, lower triglycerides and heart rate, increase brain weight by stimulation of neuroprotective mechanisms and rescue of brain vasculature, and protect brain cortices against apoptosis. The increased brain levels of GLP-1 can result from either crossing the blood-brain barrier or local production after stimulation of the vagal nerve. The increased brain levels of cGMP may protect against apoptosis. AMPK is a metabolic regulator, which prevents neuronal apoptosis and autophagic activation via the inactivation of mTOR. Exenatide can partially rescue the brain cortical AMPK levels, enhancing the autophagic pathway, which is associated with increased PI3K class III, LC3-II, Atg7, and glycosylated LAMP-1. The lower caspases activity is reinforced by higher Bcl2 levels, which is a well-known anti-apoptotic protein [7].
Exenatide is suggested to have a neuro-protective role, as it was reported to improve cognition in rats subjected to traumatic brain injury, modulate the neuroinflammatory processes, and protect against ischemic brain damage in normal and obese diabetic mice. Moreover, it was stated to protect diabetic rat brain cortices against apoptosis by increasing brain GLP-1 levels, and it was suggested to enhance the autophagic pathways by inducing the removal of toxic proteins and damaged organelles [7].

**Effects of exenatide on the autophagic function**

Interestingly, the effect of exenatide on autophagy differs between the pancreas and the brain. Regarding the pancreas, some studies reported the occurrence of pancreatitis as a side effect of exenatide administration, which was resulting from the impairment of the autophagic flux [43, 44]. However, there is a controversy on this effect of exenatide, as other studies reported that the stimulation of autophagy by GLP-1 can promote β-cell survival [45].

Exenatide can activate the brain protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K)/Akt signaling pathways, promoting autophagy, which allows clearance of misfolded proteins and damaged organelles [7]. This autophagy-enhancing effect is proven by [46], and [47], as well.

Furthermore, the chronic peripheral administration of exenatide may have a promising impact on the long-term complications of diabetes including cognitive dysfunction (Figure 4) [7].

Notably, in a parkinsonian rat model of α-synucleinopathy, exenatide was reported to improve dopaminergic degeneration, pathological α-synuclein aggregation, and behavioral deficits via promoting autophagy through the inhibition of the PI3K/Akt/mTOR pathway [48]. While in another mouse model of Parkinson’s disease, exenatide promoted autophagy through the activation of Akt pathway [49].

**Conclusion**

The dysregulation of the autophagic activity is one of the important mechanisms for hippocampal neuronal affection and diabetic cognitive dysfunction. Exenatide can modify the autophagic process through the PKA and PI3K/Akt signaling pathways, and it represents a promising therapy for the treatment of different diabetic complications for the possible beneficial effects of its long-term administration. Further research is needed to understand the exact mechanisms of the factors affecting the autophagic process and to understand the precise pathways of the therapeutic benefits of exenatide, and the probable solutions to overcome the possible side effects.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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