The Role of Insulin Receptor Signaling in Synaptic Plasticity and Cognitive Function

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Insulin is the most abundant peptidergic hormone secreted by the pancreatic islets of Langerhans and plays an important role in organic metabolism. In recent years, various functions for insulin receptor signaling in the brain have been suggested in normal neurophysiology, and a dysregulation of insulin secretion or insulin receptor signaling has been reported in serious mental illnesses. Several lines of work in both laboratory animals and humans suggest that when neurons in cognitive brain regions such as the hippocampus and cerebral cortex do not make enough insulin or cannot respond to insulin properly, everything from very mild memory loss to severe neorodegenerative diseases can result. On the other hand, administration of insulin exerts memory-enhancing action in both humans and experimental animals. Insulin has also recently been shown to regulate the endocytosis of 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, which causes long-term depression (LTD) of excitatory synaptic transmission. The fact that LTD in the mammalian brain is generally assumed to be a synaptic mechanism underlying learning during novel experiences, this insulin-induced LTD may therefore serve as an important role in brain information processesing. Recent advances in the knowledge of the biological role of brain insulin receptor signaling in relation to synaptic plasticity and cognitive function, and of the regulatory signaling mechanisms involved in these processes will be discussed in the article. *(Chang Gung Med J 2010;33:115-25)*

Key words: insulin, synaptic plasticity, cognitive function, neuron

Insulin is a peptidergic hormone composed of 51 amino acid residues normally secreted by the pancreatic islets of Langerhans in response to increasing levels of metabolic fuels in the blood. Following the discovery of insulin in 1921 by Banting and Best, major research work focused on the role of insulin in peripheral tissues (liver, muscle and adipocytes) in regulating glucose homeostasis. It is now clear that insulin receptor signaling promotes the uptake of glucose from the circulation by inducing the translocation of glucose transporters from the cytoplasm towards the plasma membrane. Glucose taken up by the transporters is then stored as glycogen, a source of energy. A defect in any of the aforementioned

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events, leading to an impaired uptake of glucose and resulting in excess glucose build-up in the blood, may cause diabetes. The most common forms of type I diabetes are characterized by an autoimmune-mediated destruction of insulin producing β cells in the pancreas, resulting in absolute insulin deficiency. Type II diabetes is characterized by insulin resistance or reduced insulin sensitivity. Both forms of diabetes can cause long-term complications such as functional changes in the retina, heart disease, kidney failure, neuropathy, eye disease, and blood vessel disease.

For a long time, it was believed that brain glucose metabolism is not dependent on insulin and therefore, the brain was classically considered to be an insulin-insensitive organ. However, there is growing evidence that insulin also has profound effects on the central nervous system (CNS). Although the expression of insulin receptors in the brain was identified decades ago,[1,2] insulin receptor function in this classically "insulin-insensitive" organ remains largely unclear. Over the past few years, the role of insulin receptor signaling in the brain has become the focus of research. Because space does not permit a full discussion of the actions of insulin receptor signaling in the brain, in this review we will highlight the putative role of insulin in the regulation of hippocampal synaptic plasticity and cognitive function based on evidence accumulated to date. Readers are referred to a number of recent comprehensive reviews for a more complete discussion of this topic.[3-7]

Brain insulin and insulin receptor signaling

Insulin exerts its effect by binding to specific receptors on the plasma membrane of cells. The insulin receptor is a tetrameric membrane spanning protein composed of two α and two β subunits, linked together by disulfide bonds.[8] The α-subunits are located entirely on the extracellular surface with a binding sites for insulin, and the β-subunits are transmembrane proteins possessing tyrosine kinase activity.[9] Binding by insulin triggers a rapid autophosphorylation of the receptors, followed by tyrosine phosphorylation of the insulin receptor substrate (IRS) protein family. Phosphorylated IRS binds to various effector molecules such as the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) via Src homology 2 (SH2) domains, and triggers activation of PI3K, which in turn activates protein kinase C (PKC) and a serine/threonine protein kinase, Akt/protein kinase B (Fig. 1). Another major signaling pathway of the insulin receptor is associated with the cytoplasmic intermediate SH2 and collagen containing protein (Shc), which links the insulin receptor with other adaptor proteins such as growth factor receptor binding protein 2 (Grb-2)/son-of-sevenless (SOS) complex. The association of the Grb-2/SOS complex with the insulin receptor via phosphorylated Shc couples the insulin receptor to Ras/Raf activation, which in turn triggers activation of mitogen-activated protein kinase (MAPK) cascades.[10]

The first demonstration of insulin receptors in the brain was reported in 1978 by Havrankova and colleagues with the use of ligand autoradiography.[1] The presence and localization of insulin receptors in the brain were subsequently confirmed by immunohistochemistry and autoradiography.[11,12] Insulin receptors are widely dispersed throughout the brain with the highest density in the olfactory bulb, cerebral cortex, hypothalamus, and hippocampus, where they are thought to subserve a number of functions including regulation of glucose metabolism, food intake and body weight, fertility and reproduction, learning, memory, and attention.[13-15] Brain insulin receptors are present in particularly high concentrations in neurons, and in much lower levels in glia.[16] Although the mRNA of insulin receptors is largely localized in neuronal somata, abundant insulin receptors are found in both cell bodies and synapses.[16,17] In the adult mammalian brain, two types of insulin receptors are found: a peripheral type found only on glial cells, and brain-specific types found on neurons.[18] However, both types appear to have similar signal transducing properties.

While the presence of immunoreactive insulin in the brain is well known, the origin of brain insulin has been a controversial issue. Whether the brain synthesizes insulin is currently debated. Although accumulated evidence indicates that brain insulin is derived from peripheral insulin and transferred in a transporter regulated way through the blood-brain barrier,[19,20] there is also evidence consistent with local synthesis of insulin in the brain. Studies revealed that insulin can be produced locally in rabbit neuronal cells from culture and from the brain.[21,22] Synthesized insulin was also shown to be secreted into the extracellular space specifically by

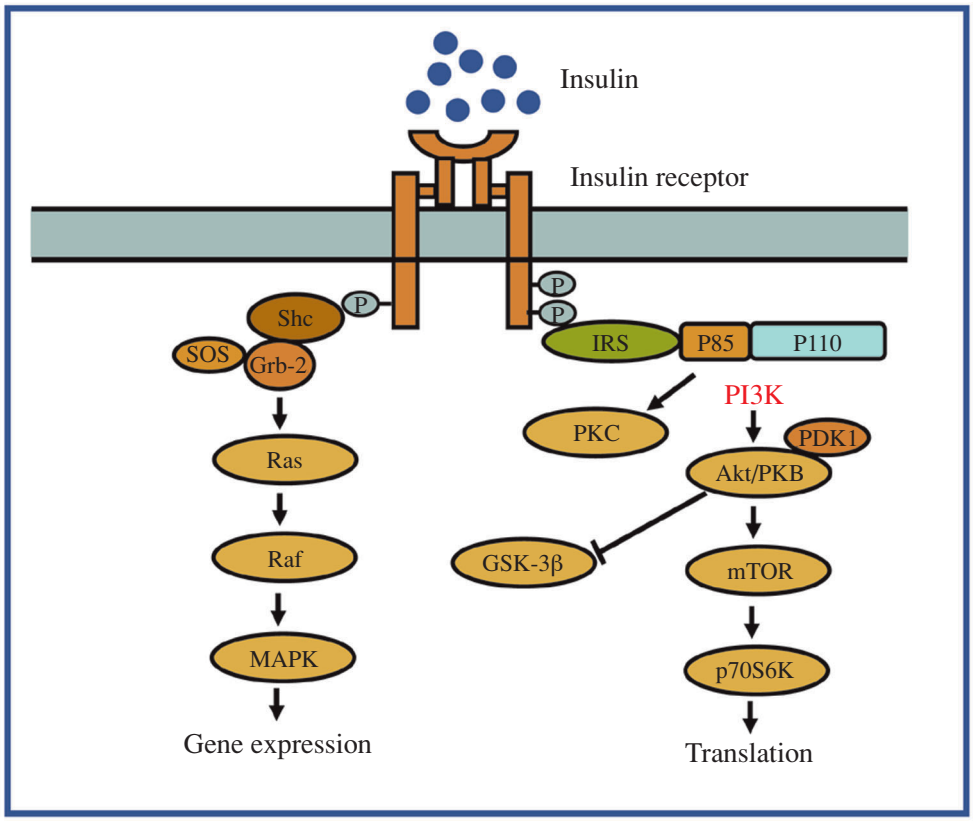

Fig. 1 The main insulin receptor signaling in neurons. Binding of insulin to extracellular insulin receptor α-subunits stimulates the tyrosine kinase activity of β-subunits, resulting in receptor autophosphorylation and subsequently, phosphorylation of intracellular insulin receptor substrate (IRS) proteins on tyrosine residue. Phosphorylated IRS binds to various effector molecules such as the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) via Src homology 2 (SH2) domains, and triggers activation of PI3K, which in turn activates protein kinase C (PKC) and serine/threonine protein kinase, Akt/protein kinase B (PKB). Another major insulin receptor signaling pathway is associated with the cytoplasmic intermediate SH2 and collagen containing protein (Shc), which links the insulin receptor with other adaptor proteins such as growth factor receptor binding protein 2 (Grb-2)/son-of-seven-less (SOS) complex. The association of the Grb-2/SOS complex with the insulin receptor via phosphorylated Shc couples the insulin receptor to Ras/Raf activation, which in turn triggers activation of mitogen-activated protein kinase (MAPK) cascades. These signals finally result in the diverse biological effects of insulin receptor signaling in the central nervous system.

neurons.[22] However, the expression data have not been confirmed in humans and other species. In addition, there is still no general agreement about actual brain insulin levels. Using an insulin radioimmunoassay strategy under resting conditions, it has been demonstrated that the concentration of immunoreactive insulin extract from whole hippocampal formations was about 0.2 ng/g wet tissue.[11] However, it remains a challenging task to demonstrate the local cerebral concentration of insulin in the brain of living animals by means of classical microdialysis and/or voltammetry techniques.

The role of insulin receptor signaling in hippocampal synaptic plasticity

Although the mRNA of insulin receptors is largely localized in neuronal somata, abundant insulin receptors are found in both cell bodies and synapses.[16,17,23] However, very little is known about the functional significance of synaptic insulin receptors in the neurons. Over recent years, several studies have drawn links between insulin receptor signaling and plasma membrane expression of ion channels as well as neurotransmitter receptors at the CNS synapses. For example, it has been shown that insulin rapidly recruits functional $GABA_A$ receptors

to postsynaptic domains in hippocampal neurons, resulting in a long-lasting enhancement of $GABA_A$ receptor-mediated synaptic transmission.[24] In addition, we and other investigators have provided evidence that insulin can promote the internalization of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors from the synaptic membrane of neurons, which causes a long-term depression (LTD) of excitatory synaptic transmission in the hippocampus and cerebellum.[25-28] Moreover, insulin enhances *N*-methyl-D-aspartate (NMDA) receptor-mediated synaptic transmission at the hippocampal CA1 synapses and potentiates the activity of recombinant NMDA receptors expressed in *Xenopus* oocytes.[29,30]

LTD is a persistent, use-dependent decrease of synaptic efficacy that, together with the converse process, long-term potentiation, (LTP), has been considered crucial for information storage in the brain and refinement of neuronal circuitry during development.[31] In our current work, using both electrophysiological and biochemical approaches, we have identified a novel form of insulin-induced LTD at the Schaffer collateral-CA1 synapses.[28] The major findings in our study were (1) a brief bath application of insulin induces LTD of excitatory synaptic transmission and that is specific to the AMPA receptor-mediated component of synaptic transmission; (2) insulin-induced LTD does not require the activation of ionotropic glutamate receptors for its induction; (3) suppression of a postsynaptic $[Ca^{2+}]_i$ increase by Ca^{2+} chelator or removal of extracellular Ca^{2+} blocks the induction of LTD by insulin; (4) the induction of LTD by insulin is not dependent on the activation of NMDA receptors, but requires the activation of L-type voltage-activated Ca^{2+} channels and the release of Ca^{2+} from functional intracellular stores; (5) the stimulation of insulin receptor tyrosine kinase leading to the activation of downstream PI3K and PKC signaling pathways is required for the induction of LTD by insulin; (6) insulin-induced LTD is expressed postsynaptically and is dependent on a rapamycin-sensitive local translation of dendritic mRNA; (7) insulin-induced LTD does not require protein phosphatase activation and is mechanistically distinct from LTD induced by low-frequency stimulation; and (8) a rapid endocytotic removal of the postsynaptic GluR2 subunit is involved in the process of insulin-induced LTD formation. Our results suggest that PI3K/PKC-dependent insulin receptor signaling, which controls synaptic surface expression of AMPA receptor numbers through protein phosphatase-independent endocytosis, may be a major expression mechanism of insulin-induced LTD in hippocampal CA1 neurons (Fig. 2). Although the physiological consequences of insulin-induced LTD remain an open question, LTD in the mammalian brain is generally assumed to be a synaptic mechanism underlying learning during novel experiences,[32,33] and an immunoblotting study has demonstrated that insulin receptor function is clearly up-regulated in the hippocampal CA1 and dentate gyrus regions shortly after water maze spatial training.[34] Therefore, this insulin-induced LTD may serve an important role in hippocampal information processing.

The postsynaptic density (PSD) is a specialization of cytoskeleton at the synaptic junction and serves as an important organizer of the postsynaptic signal transduction machinery.[35] The PSD forms a disc that consists of cytoskeletal and regulatory proteins, some of which contact the cytoplasmic domains of ion channels or neurotransmitter receptors in the postsynaptic membrane.[36] One of the fundamental structural proteins within the PSD is PSD-95, a 95-kDa scaffolding protein containing multiple PSD-95/Discs large/zona occluens-1 domains to anchor and associate glutamate receptors with other functional proteins in the PSD.[37,38] Although the function of the PSD-95 protein at the synapses is not yet clear, evidence from PSD-95 mutant or expression studies has demonstrated that PSD-95 may play a modulatory role in control of synaptic transmission,[39] bidirectional synaptic plasticity,[40] maturation of excitatory synapses,[39] and drug addiction.[41] Our recent study has indicated that brief insulin treatment substantially increases the synthesis of PSD-95 protein in local dendritic compartments via activation of the PI3K-Akt-mammalian target of the rapamycin (mTOR) signaling pathway.[42] Insulin activates mTOR and its downstream translation regulatory molecules, 4E-BP1 and p70S6K, to stimulate the translation of the dendritic spine scaffolding protein PSD-95 (Fig. 3). We also demonstrated that insulin stimulates the translation of PSD-95 in a transcription-independent manner. The physiological significance of insulin-induced increases in dendritic PSD-95 protein synthesis remains to be elucidated. Given

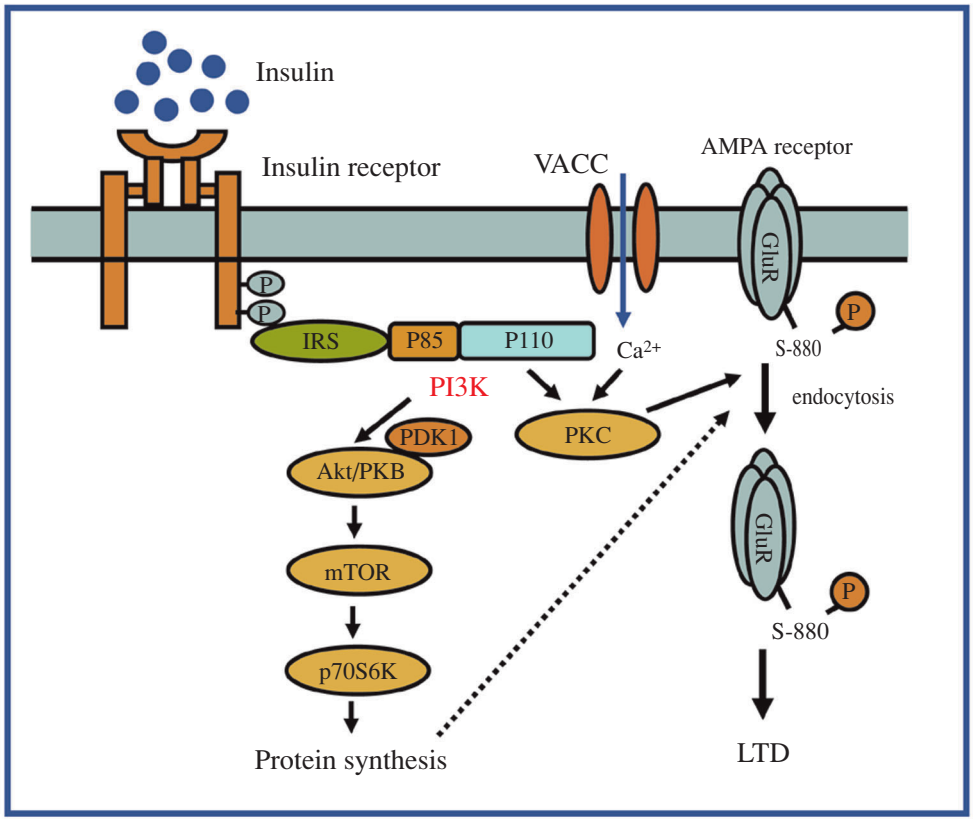

Fig. 2 A working model of the induction of long-term depression by insulin at the Schaffer collateral-CA1 synapses. Insulin-induced LTD is induced and expressed postsynaptically and requires the following three signaling events: (1) a PI3K/PKC-dependent signaling process that controls the endocytotic removal of AMPA receptor GluR2 subunits from the postsynaptic surface membrane; (2) a mammalian target of rapamycin (mTOR)/p70S6K-mediated local protein synthesis at synaptic sites; and (3) a rise in postsynaptic $[Ca^{2+}]_i$, possibly mediated by an increase of Ca^{2+} entry through L-type voltage-activated Ca^{2+} channels (VACC) as well as the release of Ca^{2+} from intracellular stores. Insulin-induced LTD requires a PKC-dependent phosphorylation of the GluR2 subunit at Ser-880 and is mediated by GluR2 subunit endocytosis.

that the PSD-95 protein is generally assumed to be an adapter molecule to cluster ion channels and neurotransmitter receptors or organize a signaling complex at the postsynaptic membrane,[38] and that considerable evidence implicates a chaperone role for PDZ-containing proteins in the early events of assembly, processing, and delivery of receptor proteins, this event may therefore serve an important role in controlling synaptic strength and plasticity.

In addition to modulation of synaptic plasticity, insulin has also been reported to regulate structural plasticity, the predominant mechanisms for changes in the network architecture in the brain. Dendritic spines are small protrusions arising from the dendrites that form the postsynaptic compartments for excitatory inputs.[37] These small protrusions show actin-based rapid motility, dynamic turnover and morphological plasticity.[43-46] Changes in the structure and number of dendritic spines have been generally proposed to contribute to numerous physiological processes such as synapse development, function and plasticity.[47-50] More recently, the crucial roles of insulin receptor signaling in the development and maintenance of excitatory synapses within the *Xenopus* retinotectal circuit have been revealed.[51] Recent work from our laboratory also identified an important role of insulin receptor signaling in the regulation of dendritic spine and excitatory synapse formation in cultured hippocampal neurons *in vitro*. Our results support a model in which insulin acting

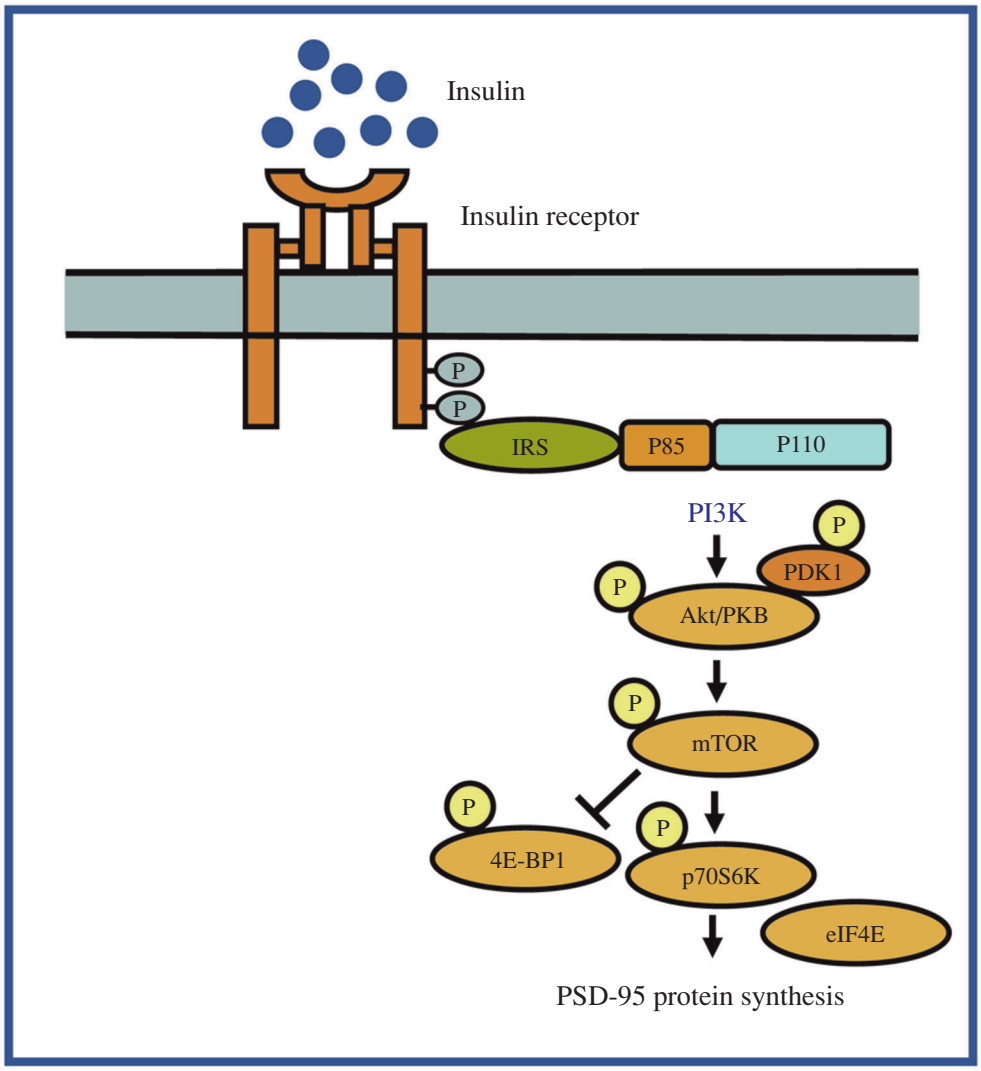

Fig. 3 A working model of the insulin-induced increase in PSD-95 protein expression in hippocampal area CA1. Binding of insulin to insulin receptors stimulates dendritic translation machinery through a PI3K/Akt/mTOR signaling pathway. Insulin activates mTOR and its downstream translation regulatory molecules, 4E-BP1 and p70S6K, to stimulate the translation of the dendritic spine scaffolding protein PSD-95.

on insulin receptors activates the PI3K-Akt-mTOR signaling pathway, which in turn promotes Ras-related C3 botulinum toxin substrate 1 (Rac1)-dependent actin cytoskeletal rearrangement and dendritic spine formation. These findings add to the growing list of functions for insulin receptor signaling in neuronal development and synaptic plasticity. Taken together, these results suggest that insulin receptor signaling may regulate not only the processing of synaptic plasticity but also the structural plasticity by cytoskeletal rearrangement that is required for the incorporation of neurons into brain circuits.

The role of insulin receptor signaling in cognitive function

A novel function of insulin receptor signaling in the CNS is its role in cognitive activity. Although still at an early stage, efforts in behavioral and biochemical studies have begun to uncover the cellular and molecular basis for brain insulin receptor signal-

ing in learning and memory processing. In human subjects, it is widely documented that both type 1 and type 2 diabetes are associated with cognitive impairment and an increased risk of dementia and Alzheimer's disease, especially in older patients.[52] A number of well-designed epidemiological studies have also indicated that hyperinsulinemia is a risk factor for dementia,[53,54] whereas insulin administration to Alzheimer's disease patients to keep glycemic levels constant can improve memory formation.[55,56] In addition, systemic administration of insulin under euglycemic hyperinsulinemic conditions in healthy humans yields a significant improvement in verbal memory and selective attention.[57] In experimental animals, administration of insulin into the third cerebral ventricles of rats shortly after a passive avoidance training experience resulted in higher memory retention levels compared with rats that received saline.[58] Perfomance in the Morris water maze was clearly impaired in animals with streptozotocin-induced diabetes compared with non-diabetic animals.[59,60] All of these results suggest a link between brain insulin receptor signaling and congnitive functions such as learning and memory.

It is interesting to note the role of brain insulin receptor signaling in neurodegenerative disorders. Research in recent years has significantly advanced our knowledge about this important issue. Alzheimer's disease is the most common neurodegenerative disorder in humans. One of the earliest clinical manifestations in Alzheimer's disease patients is a profound loss of memory. Two of the neuropathological hallmarks of Alzheimer's disease are numerous senile plaques and neurofibrillary tangles in the affected brain regions.[61] Neurofibrillary tangles are intracellular accumulations of paired helical filaments that are assembled from microtubule-associated protein tau, and amyloid plaques are compact areas of degenerating neuritis surrounding a core amyloid-β protein (Aβ), which is a 40-42 amino acid peptide derived by proteolysis of type I transmembrane amyloid-β precursor protein.[62-64] Interestingly, individuals suffering from Alzheimer's disease have lower cerebrospinal fluid and higher plasma insulin levels than healthy age-matched subjects,[65] which could indicate an impairment in brain insulin action. In line with this hypothesis, administration of insulin to individuals with Alzheimer's disease has been shown to result in an improvement in memory and performance.[66,67] It has also been reported that insulin can protect cultured hippocampal neurons and human brain pericytes against Aβ-induced cytotoxicity, suggesting that insulin and Aβ may interact with each other.[68-70] This hypothesis is supported by a study showing that Aβ can compete for binding of insulin to its insulin receptor, resulting in a decrease in insulin receptor-mediated signaling.[71] In addition, a very recent study has revealed that insulin can inhibit Aβ binding to cultured hippocampal neurons and prevent Aβ-induced loss of insulin and NMDA receptors.[69] However, it is not clearly known whether this effect is related to a binding of Aβ to insulin or directly to the insulin receptor.[70] Because Aβ and insulin are both amyloidogenic peptides sharing a consensus sequence for degradation by insulin-degrading enzyme,[72] insulin may ameliorate the deleterious effects of Aβ by modulating Aβ aggregation. Furthermore, insulin may also regulate the extracellular concentration of Aβ by inhibiting insulin-degrading enzyme degradation of Aβ or by stimulating Aβ secretion.[73] Recently, Xie et al. reported that Aβ competes for binding of insulin to the insulin receptor *in vitro*.[71] More recently, we extended these findings by demonstrating a direct interaction between Aβ and insulin peptides *in vitro*. Our data showed that insulin is capable of inhibiting synthetic Aβ assemblies and ameliorates Aβ-induced impairment of LTP in the CA1 region of rat hippocampal slices.[74] Furthermore, insulin receptor signaling may also regulate the extracellular concentration of Aβ by inhibiting insulin-degrading enzyme degradation of Aβ or by stimulating Aβ secretion.[74] These observations open new directions for research in Alzheimer's disease and suggest a therapeutic avenue that might be effective in ameliorating the synaptic dysfunction in the earliest stages of the disease.

Conclusions

Studies over the past few years have provided only preliminary insight into the role of insulin receptor signaling in the brain, which includes regulation of synaptic plasticity and cognitive function. Although the molecular mechanisms underlying these processes are not clearly understood, they seem to involve the activation of PI3K and MAPK signaling pathways. Furthermore, these mechanisms may be independent of its direct glucose regulation in the

periphery. Since increasing evidence suggests a contribution of abnormalities in brain insulin receptor signaling in the origin of cognitive decline and the development of neurodegenerative disorders, the administration of insulin may be useful as a novel therapeutic strategy in the treatment of Alzheimer's disease and CNS pathologies that involve cognitive impairment. Since peripheral insulin administration may have undesirable metabolic side effects such as induction of hypoglycemia and insulin resistance, the development of a novel treatment strategy to dissociate the central and peripheral effects of insulin is important for future studies. In this regard, a recent clinical trial study has shown that intranasal insulin delivery allows insulin to bypass the blood-brain barrier to the CNS without changing plasma glucose or insulin levels.[67] However, the long-term efficacy and safety of intranasal insulin delivery need further investigation.

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胰島素受體訊息在神經突觸塑性及認知功能中所扮演之角色

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胰島素 (insulin) 爲一種體內富含的肽能激素 (peptidergic hormone)，其主要由胰臟的蘭氏小島 (islets of Langerhans) β型分泌細胞所製造及分泌，並且在身體的代謝功能的執行上扮演著相當重要的角色。近年來的研究顯示，中樞神經系統中也富含著胰島素受體傳遞訊息，並且當此傳遞訊息發生缺損時會發生嚴重的精神性障礙及疾病 (mental illnesses)。許多實驗動物及人體實驗證據指出，當腦中參與認知功能表現的區域如海馬迴 (hippocampus) 及大腦皮質區域 (cerebral cortex) 的神經元無法獲取足夠的胰島素或產生適當的胰島素受體傳遞訊息時，會造成記憶形成的能力下降，嚴重者甚至會發生腦部神經元退化的情形。反之，直接投與胰島素對於實驗動物及人類會產生促進記憶形成的作用。近年來，胰島素也被發現會促進 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) 型式的麩胺酸受體產生內吞作用 (endocytosis)，進而誘發長期抑制現象 (long-term depression, LTD) 的發生及表現。由於長期抑制現象已知可能參與新穎經驗記憶的形成，因此胰島素所誘發之長期抑制現象可能與腦部神經訊息傳遞及記憶形成的過程有關。本篇論文主要的目的在於整理及討論近年來有關腦中胰島素受體傳遞訊息參與神經突觸塑性及認知功能表現的相關研究進展。(長庚醫誌 2010;33:115-25)

關鍵詞：胰島素，神經突觸塑性，認知功能，神經元

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