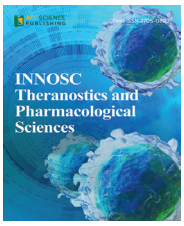
INNOSC Theranostics and Pharmacological Sciences 2021 Vol. 4 (No. 2) pp: 17-21

ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

Journal homepage: https://accscience.com/journal/ITPS



REVIEW ARTICLE

Role of Insulin in Brain: An Emphasis on Molecular Functions

Snehashis Kundu[1], Sayeed Mohammed Firdous[2]*

[1]National Institute of Pharmaceutical Education and Research Guwahati, Changsari, Assam, India

[2]Department of Pharmacology, Calcutta Institute of Pharmaceutical Technology and AHS, Howrah, West Bengal, India

Corresponding Author:** Sayeed Mohammed Firdous, ***Email: firdous.oncology@gmail.com

Received: March 8, 2022; ***Accepted***: May 23, 2022; ***Published***: June 30, 2022 *DOI:* 10.36922/itps.v4i2.43

Copyright: Author(s). This is an open-access article distributed under the terms of the Attribution Non-Commercial 4.0 International 4.0 (CC BY-NC 4.0), which permits all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract:

Insulin signaling in brain has emerged as a recent field of research since decreased brain insulin levels were linked to impaired learning, memory, and neurodegenerative diseases like Alzheimer's disease. Brain insulin has a pivotal role in regulating glucose metabolism, memory, learning, neuron formation, and to be neuroprotective through a cascade of cellular signaling process. In addition, insulin may serve as a promising therapy against diabetes and neurodegeneration conditions. Interestingly, insulin has been also faced as the potential missing link between neurodegenerative disorders and diabetes. Therefore, this review aims to untangle the complex interactions among aging and diabetes which allow the development of more effective therapeutic strategies to conquer neurodegenerative condition as well as diabetes.

Keywords: Insulin, Memory, Learning, Neurodegenerative diseases, Aging, Diabetes

1. Introduction

Insulin is an anabolic peptide hormone produced by the beta cells of the pancreas' Islets of Langerhans. It has a significant impact on the breakdown of carbohydrates, proteins, and fats. Furthermore, it promotes the synthesis of glucagon, triacylglycerols, and proteins in human body. This hormone has been implicated for diabetes mellitus therapy. It holds a unique place in the history of both biochemistry and healthcare. It was the first hormone to be extracted, refined, synthesized, and decoded. Recombinant DNA technology (rDNA) can also be used to produce insulin [1]. Until today, insulin and its signaling process are still at the forefront of medical research and discoveries, from bench to bedside and to the public health policy [2]. The functions of insulin are presented in the **Figure 1.** Insulin is transported across the blood-brain barrier to the brain by specialized carriers. Insulin receptors (IR) are abundantly generated as well as dispersed throughout the brain, with IR-A variant predominating over the longer, better noticeable IR-B variant present throughout the human body. Insulin binds to IR-A, which causes autophosphorylation and activation of the receptor. This causes IR substrate (IRS) proteins to be phosphorylated downward that are involved in a range of cells signaling cascades.

Many scientists have demonstrated that insulin plays a primary role in neuroprotection. Besides, it provides support to memory formation and neuronal development, as well as glucose metabolism in neuronal cells that involved a cascade of cellular signaling molecules. Based on these facts, it has been recognized that insulin in the future could have a key role in the treatment of artifacts of neurons.

©2021 AccScience Publishing

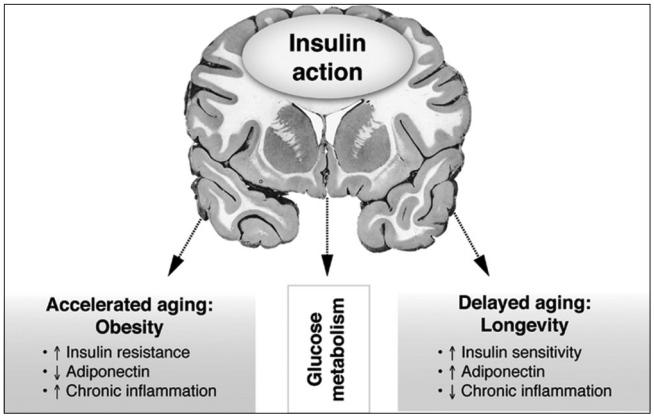


Figure 1. Functions of insulin.

Hence, in this review, we attempt to consolidate the functions of insulin in neuronal cells.

2. Signaling pathway mediated by IR/insulin growth factor-1 receptors (IGF-1R) in neurons

2.1. IR/IGF-1R localization in the brain

Insulin rapidly binds to IR once in the brain. These IRs are highly abundant throughout CNS [3], mainly in hypothalamus, cerebellum, hippocampus, olfactory bulb, striatum, and cerebral cortex [4]. The differential distribution of IR and insulin in brain indicates that insulin from various sources (local or peripheral) may reach IR from different brain regions to begin neural signal transduction [5]. IR is largely present in neurons especially in the synapses and cell bodies than in glia [6-10]. Likewise, IGF-1Rs are found throughout neurons and glia, especially in hippocampus, cerebellum, amygdala, cerebral cortex, parahippocampal gyrus, and caudate nucleus. The less amount of IGF-1R is present in the substantia nigra, cerebral peduncles, and white matter.

2.2. Brain IR/IGF-1R structure and signaling pathway

Both IGF-1R and IR are tetrameric glycoproteins that belong to the family of tyrosine kinases. They were made up of two alpha subunits (120 – 135 K Da) and two beta subunits (95 K Da) [11]. IR subunits in brain vary from peripheral because they have slightly lower molecular weight as well as lack of downregulation after exposure to high insulin levels. In the mammalian brain, two types of IR have been discovered: A "peripheral"-like type (with less glia cells) and a neuron-specific type (largely expressed in neurons). Insulin and IGF-1 connect to both IR and IGF-1R due to structural and functional similarities, with insulin binds to the IR with higher affinity than IGF-1, whereas IGF-1R predominantly attaches IGF-1 compared to insulin.

When insulin binds to α subunits of brain IR or IGF-1R, it leads to autophosphorylation of β subunits at tyrosine residues of the receptor. Furthermore, IRS docking proteins are phosphorylated at tyrosine residues. Signaling components (particularly p85 regulatory subunits of phospatidylinesitol 3-kinase PI3K) are retrieved from the Src homology2 (SH2) domain and activate growth factor receptor bound protein 2 (Grb-2) and the PI3K subunit. As a result, the PI3K/Akt/glycogen synthase kinase-3 (Gsk-3) and Ras/Raf-1/extracellular signal regulated kinas (ERK1 and ERK2, ERK1/2) signaling pathways [12-14] can be activated.

2.3. PI3K/Akt signaling cascade

After binding of the p85 SH_2 domain to the active IRS, PI3K becomes active while p110 inhibition is relived. Active PI3K is translocated into plasma membrane and subsequent formation of PI-3,4,5-triphosphate and PI-3,4-biphosphate occurred. These molecules then attach to and recruit downstream signaling proteins comprising of pleckstrin homology domains. Protein kinase 3-phosphorisitide dependent protein kinase-1 phosphorylates the serine (Ser)/threonine (Thr) kinase Akt which has been recruited to the plasma membrane. Once triggered, Akt detaches from cell membrane and translocates into the cytosol and nucleus in which it phosphorylates target proteins at Ser and Thr residues. Proapoptotic proteins, Bad, and GSK-3 are among the targeted proteins. Hence, it can be inferred that Akt activation suppresses apoptosis [15].

2.4. SHC/ERK1/2 signaling pathway

When IR becomes phosphorylated, Src homology-2 domain containing (SHC), an adapter protein binds to IR and Grb2 binds SHC through its SH2 domains, which activates ERK1/2 signaling pathway. SH3 domains interact with son of sevenless protein and this interaction stimulates the exchange from GDP to GTP at Ras, which then becomes active and recruits the Ser/Thr kinase Raf. Subsequent activation of MEK or mitogen activated protein

©2021 AccScience Publishing

kinase (MAP2K) leads to phosphorylation (and activation) of ERK1/2 [16], which causes activation of numerous transcription factors (Ets-like protein-1 and c-Myc) [14] that control gene expression.

Importantly, ERK1/2 activation plays an antiapoptotic role in neurons through the phosphorylation of Bad at Ser112 [17,18]. In contrast, other studies found that oxidative distress and certain action excreted by the N-methyl D-aspartate receptor contribute to activated Erk1/2 in synaptic plasticity and cell death.

3. Role of insulin and IGF-1 in brain

3.1. Glucose metabolism

Insulin/IGF-1 mediated IR/IGF-1R signaling pathways could play an important role in CNS functions such as brain metabolism management [19-22], neuronal development and division, and neuromodulation. The deficiency of insulin due to some damaging conditions leads to cell atrophy and apoptotic death. Thus, it proves that tissue (and cellular) is dependent on insulin.

Insulin regulates glucose transportation and utilization in the peripheral body [23]. Hormonal peripheral and nutritional signals are coordinated and they are regulated by neurons in the hypothalamus. Peripheral signals for energy homeostasis and ingestive behavior are controlled by these neurons. Apart from insulin, anorexigenic peptides proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript, orexigenic neuropeptide Y (NPY), and agouti-related peptide (AgRP) are also involved [24]. Under supraphysiological blood glucose levels, brain insulin causes glucosing neurons to hyperpolarize, activating K^+ ATP channels and lowering neuronal activity (due to the inactivation of POMC neurons), resulting in weight loss. Moreover, the deprivation of insulin signaling in brain activates JNK and phosphorylates IRS-1 at Ser/Thr. This promotes a feedback inhibition of IR. As a result, body weight is increased. The activation of arcuate neurons, which contain NPY, AgRP, and GABA, causes orexigenic effect [25].

Neuronal insulin/IR signaling pathways can regulate glucose metabolism in the brain. This is supported by the overlapping distributions of insulin, IR, and glucose transporters (GLUTs) isoforms 1 and 4 in certain brain areas (e.g., hippocampus and choroid plexus). According to Binghom *et al*. [26], fasting insulin levels increase global glucose metabolism maximally in the human brain cortex, either directly (as in peripheral tissues) or obliquely (as in peripheral tissues) through insulin-mediated neuronal activation. These authors proposed that if the recruitment of GLUTs into the plasma membrane and the resulting increase in glucose uptake was a direct effect of insulin, partially insulin-sensitive glia GLUT1 might be responsible for this effect since the main neuronal GLUT3 is insulin insensitive.

Insulin can provide energy for neurons by inhibiting neuronal norepinephrine absorption, followed by activation of glia-adrenoreceptors and glucose extrusion from glia1 glycogen stores, particularly in astrocytes. As a result, astrocytic glycogen can be converted to glucose where it is then transported to the extracellular fluid by GLUT1 [27]. Taken together, this evidence suggests that any harmful interference between insulin and neuronal glucose metabolism may impair ATP synthesis and causes neuronal apoptosis [28].

4. Other actions of insulin

4.1. Synaptic transmission and memory/learning

Outgrowth and renewal of myelinated fibers are both increased by brain insulin. It maintains cortical, sympathetic, and sensory neuronal survival and stimulates neuronal protein synthesis. It also improves synaptic activity and plasticity, memory format, and storage, as well as neuroprotection. It has been shown that administration of insulin in rats as well as in humans (intranasal route) improves their memory without any peripheral glycemia. Attention and verbal memory also improved by systemic insulin infusion [29]. These results correlate with high IR expression in hypothalamus and limbic system. It is an important effect of insulin for synaptic transmission (e.g., monoamines) [30,31]. About 30 years ago, insulin was discovered to boost epinephrine and non-epinephrine release in adrenergic terminals, block non-epinephrine synaptic reuptake, change catecholamine kinetics, and stimulate neuronal serotonin uptake. Insulin influenced the expression of IVMOA receptors, according to some scientists,

©2021 AccScience Publishing

by enhancing neuronal $Ca2^{+}$ influx and reinforcing synaptic connection between neurons. Insulin also influenced the long-term potentiation of a molecular learning model. This is supported by insulin-mediated control of glutamate and GABA receptor density which affect the synaptic plasticity. The neuromodulatory effect of insulin could be due to its direct effect on neurotransmitter transport through lower ATP levels and subsequent reversal of the amino acid transporters [32,33], which protect neurons from excitotoxicity or oxidative stress.

4.2. Neuroprotective action of insulin

The neuroprotective effect of insulin could be achieved by the restoration of IR/IGF-1R signaling-mediated gene transcription. For example, hexokinase-II and Bcl-2 are upregulated while glutathione peroxidase and caspase-3 are downregulated during IR/IGF-1R signaling-mediated gene transcription [34]. As a result, both neuronal glucose metabolism and antioxidant defenses are improved.

Others proposed that IGF-1 activates IGF-1R/PI-3K/Akt signaling pathway and prevents caspase activation through the phosphorylation of CREB (activated), GSK-3β (proapoptotic), and Forkhead box-1 (FoxO1, inactivated) [35,36]. Insulin-induced antiapoptotic effect might also arise from neural SAPK inhibition. In addition, insulin induces radical formation and lipid oxidation which are responsible for necrosis. Insulin has neuroprotective action against some damaging conditions that include oxidative stress and alleviation of neuronal apoptotic death. Such damaging conditions may generate brain dysfunction and causes several pathological conditions such as diabetes and age-related diseases such as Alzheimer's disease (AD) [37,38].

5. Conclusion, future prospects, and current findings

This review provides a better concept on the central role of insulin. Insulin plays a primary role in neuroprotection, memory formation, and neuronal development as well as glucose metabolism in brain which involved a cascade of cellular signaling molecules. Thus, insulin in the future can play a key role for the treatment of neurological disorders.

Insulin signaling in brain has sparked a lot of interest in neuroscience research over the past few decades, whether it is to understand how it works or to find a diabetes treatment. It has been recognized that the plenty of insulin and IR in brain as well as their effective involvement is required for recovery of neurodegenerative diseases and diabetes. The key goal for the next two decades will be to decipher the complex realities surrounding ageing and diabetes, as well as to develop more effective therapeutic techniques to combat neurodegenerative diseases and diabetes.

In the present literature, we found that AD is much more common in those who have diabetes. The hippocampus expresses insulin and IR signaling products. Insulin has a variety of functions in the brain. The curative usefulness of insulin as well as the function of IR signaling in AD development has received a lot of attention. It has been revealed that the cumulative insulin activity in the nervous system is in accordance with the main AD pathogenic determinants, highlights important aspects in the AD brain, but also evaluates the medicinal qualities of insulin and insulin-sensitizing medications. Insulin promotes brain growth and survival, inhibits the Tau phosphorylation kinase glycogen synthase kinase 3, and suppresses amyloidogenic processing of the amyloid precursor protein. Systemic metabolism is regulated by central nerve IR signaling, which enhances glucose supply.

Acknowledgments

Not applicable.

Funding

Not applicable.

Conflict of interest

No conflict of interest declared.

References

[1] Satyanarayana, U.; Chakrapani, U. Biochemistry Book. 5th ed. New Delhi: Elsevier Publisher, **2017**. p. 641–2.

[2] Bliss, M. The History of Insulin. Diabetes Care, **1993**, 16(3), 4–7.

[3] Zhao, W.; Chen, H.; Xu, H. Brain Insulin Receptors and Spatial Memory. Correlated Changes in Gene Expression, Tyrosine Phosphorylation, and Signaling Molecules in the Hippocampus of Water Maze Trained Rats. J. Biol. Chem., **1999**, 274(49), 34893–902.

[4] Salkovic-Petrisic, M.; Hoyer, S. Central Insulin Resistance as a

©2021 AccScience Publishing

Trigger for Sporadic Alzeheimer-Like Pathology: An Experimental Approach. J. Neural Transm., **2007**, 72, 217–33.

[5] Zhao, W.Q.; Chen, H.; Quon, M.J.; Alkon, D.L. Insulin and the Insulin Receptor in the Experimental Models of Learning and Memory. Eur. J. Pharmacol., **2004**, 490(1-3), 71–81.

[6] Baskin, D.G.; Sipols, A.J.; Schwartz, M.W.; White, M.F. Immunocytochemical Detection of Insulin Receptor Substrate-1 (IRS-1) in Rat Brain: Colocalization with Phosphotyrosine. Regul. Pept., **1993**, 48(1-2), 257–66.

[7] Schwartz, M.W.; Figlewicz, D.P.; Baskin, D.G.; Woods, S.C.; Porte, D. Jr. Insulin in the Brain: A Hormonal Regulation of Energy Balance. Endocr. Rev., **1992**, 13(3), 387–414.

[8] Marks, J.L.; King, M.G.; Baskin, D.G. Insulin and Insulin- Like Growth Factors in Molecular Biology and Physiology of Insulin and Insulin-Like Growth Factors. Adv. Exp. Med. Biol., **1991**, 293, 459–70.

[9] Unger, J.W.; Moss, A.M.; Livingston, J.N. Immunohistochemical Localization of Insulin Receptors and Phosphotyrosine in the Brainstem of the Adult Rat. Neurosci., **1991**, 42(3), 853–61.

[10] Marks, J.L.; Maddison, J.; Eastman, C.J. Subcellular Localization of Rat Brain Insulin Binding Sites. J. Neurochem., **1988**, 50(30), 774-781.

[11] Schulingkamp, R.J.; Pagan, T.C.; Hung, D.; Raffa, R.B. Insulin Receptors and Insulin Action in The Brain: Review and Clinical Implications. Neurosci. Biobehav. Rev., **2000**, 24(8), 855–72.

[12] Wada, A.; Yokoo, H.; Yanagita, T.; Kobayashi, H. New Twist on Neuronal Insulin Receptor Signaling in Health, Disease, and Therapeutics. J. Pharmacol. Sci., **2005**, 99(2), 128–43.

[13] Moloney, A.M.; Griffin, R.J.; Timmons, S.; O'Connor, R.; Ravid, R.; O'Neill, C. Defects in IGF-1 Receptor, Insulin Receptor and IRS1/2 in Alzheimer's Disease Indicate Possible Resistance to IGF-1 and Insulin Signaling. Neurobiol. Aging, **2010**, 31(2), 224–43.

[14] Van der Heide, L.P.; Ramakers, G.M.J.; Smidt, M.P. Insulin Signaling in the Central Nervous System: Learning to Survive. Prog. Neurobiol., **2006**, 79(4), 205–21.

[15] Erol, A. An Integrated and Unifying Hypothesis for the Metabolic Basis of Sporadic Alzheimer's Disease. J. Alzheimer's Dis., **2008**, 13(3), 241–53.

[16] Ogata, T.; Iijima, S.; Hoshikawa, S. Opposing Extracellular Signal-Regulated Kinase and Akt Pathways Control Schwann Cell Myelination. J. Neurosci., **2004**, 24(30), 6724–32.

[17] Johnson-Farly, N.N.; Travkina, T.; Cowen, D.S. Cumulative Activation of Akt and Consequent Inhibition of Glycogen Synthase Kinase-3 by Brain-Derived Neurotrophic Factor and Insulin-Like Growth Factor-1 in Cultured Hippocampal Neurons. J. Pharmacol. Exp. Ther., **2006**, 316(3), 1062–9.

[18] Hetman, M.; Kanning, K.; Cavanaugh, J.E.; Xia, Z. Neuroprotection by Brain- Derived Neurotrophic Factor is Mediated by Extracellular Signal-Regulated Kinase and Phosphatidyalinositol 3-Kinase. J. Biol. Chem., **1999**, 274(32), 22569–80.

[19] Gasparini, L.; Xu, H. Potential Role of Insulin and IGF-1 in Alzheimer's Disease. Trends Neurosci., **2003**, 26(8), 404–6.

[20] Santos, M.S.; Pereira, E.M.; Carvaho, A.P. Stimulation of Immunoreactive Insulin Release by Glucose in the Rat Brain Synaptosomes. Neurochem. Res., **1999**, 24(1), 33–6.

[21] Shah, B.H.; Hausman, R.E. Effect of Insulin on GABAergic Development in the Embryonic Chick Retina. Brain Res. Dev. Brain Res., **1993**, 72(2), 151–8.

[22] Yang, J.W.; Raizada, M.K.; Fellows, R.E. Effects of Insulin on Cultured Rat Brain Cells: Stimulation of Ornithine Decarboxylase Activity. J. Neurochem., **1981**, 36(3), 1050–7.

[23] Levin, B.E. Factors Promoting and Ameliorating the Development of Obesity. Physiol. Behav., **2005**, 86(5), 633–9.

[24] Levin, B.E. Metabolic Sensing Neurons and Control of Energy Homeostasis. Physiol. Behav., **2006**, 89(4), 486–9.

[25] Plum, L.; Belgardt, B.F.; Bruning, J.C. Central Insulin Action in Energy and Glucose Homeostasis. J. Clin. Invest., **2006**, 116(7), 1761–3.

[26] Bingham, E.M.; Hopkins, D.; Smith, D. The Role of Insulin in Human Brain Glucose Metabolism: An 18fluorodeoxyglucose Positron Emission Tomography Study. Diabetes, **2002**, 51(12), 169–78.

[27] Ghosh, A.; Yuk, Y.C.; Mansfield, B.C.; Chou, J.Y. Brain Contains a Functional Glucose 6-Phosphate Complex Capable of Endogenous Glucose Production. J. Biol. Chem., **2005**, 280(12): 11114–9.

[28] Russell, J.W.; Golovoy, D.; Vincent, A.M. High Glucose- Induced Oxidative Stress and Mitochondrial Dysfunction in Neurons. FASEB J., **2002**, 16(13), 1738–48.

[29] Kern, W.; Peters, A.; Fruehwald-Schultes, B.; Deininger, E.; Born, J.; Fehm, H.L. Improving Influence of Insulin on Cognitive Functions in Humans. Neuroendocrinol, **2001**, 74(4), 270–80.

[30] Boyd, F.T.; Clarke, D.W.; Raizada, M.K. Insulin Inhibits Specific Norepinephrineuptake in Neuronal Cultures from Rat Brain. Brain Res., **1986**, 398(10), 1–5.

[31] Barbaccia, M.L.; Chuang, D.M.; Costa E. Is Insulin are Neuromodulator? Adv. Biochem. Psychopharmacol., **1982**, 33, 511–8.

[32] Duarte, A.I.; Santos, M.S.; Seica, R.; Oliveira, C.R. Oxidative Stress Effects Synaptosomal Γ-Amino Butyric Acid and Glutamate Transport in Diabetic Rats: The Role of Insulin. Diabetes, **2004**, 53(8), 2110–6.

[33] Duarte, A.I.; Santos, M.S.; Seica, R.; de Oliveira C.R. Insulin Affects Synaptosomal GABA and Glutamate Transport Under Oxidative Stress Condition. Brain Res., **2003**, 977(1), 23–30.

[34] Duarte, A.I.; Santos, P.; Oliveira, C.R.; Santos, M.S.; Rego, A.C. Insulin Neuroprotection against Oxidative Stress is Mediated by Akt and GSK-3β Signaling Pathways and Changes in Protein Expression. Biochem. Biophys. Acta. **2008**., 1783(6), 994–1002.

[35] Chin, P.C.; Majdzadeh, N.; D'Mello, S.R. Inhibition of GSK 3β is a Common Event in Neuroprotection by Different Survival Factors. Mol. Brain Res., **2005**, 137(1-2), 193–210.

[36] Leinnimger, G.M.; Backus, C.; Uhler, M.D.; Lentz, S.I.; Feldman, E.L. Phosphotidylinositol 3-Kinase and Akt Effectors Mediate Insulin-Like Growth Factor-I Neuroprotection in Dorsal Root Ganglia Neurons. FASEB J., **2004**, 18(13), 1544–6.

[37] Ryu, B.R.; Ko, H.W.; Jou, I.; Noh, J.S.; Gwag, B.J. Phosphatidylinositol3- Kinase- Mediated Regulation of Neuronal Apoptosis and Necrosis by Insulin and IGF-I. J. Neurobiol., **1999**, 39(4), 536–6.

[38] Noh, K.M.; Lee, J.C.; Ahn, Y.H.; Hong, S.H.; Koh, J.Y. Insulin-Induced Oxidative Neuronal Injury in Cortical Culture: Mediation by Induced N- Methyl-D-Aspartate Receptors. IUBMB Life, **1999**, 48(3), 263–9.

Publisher's note

AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

©2021 AccScience Publishing