

Brain insulin circuit. From the basics to impact on the clinic

Circuito insulínérgico cerebral. De las bases a su impacto en la clínica

Martín de J. Sánchez-Zúñiga^{1*}, Raúl Carrillo-Esper², Herlinda Sánchez-Pérez¹,
Antonio González-Chávez³, and Sandra Elizondo-Argueta⁴

¹Intensive Therapy Unit, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra; ²Critical Areas Division, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra; ³Asociación Mexicana para el Estudio Multidisciplinario del Síndrome Metabólico, A.C., Hospital General de México Dr. Eduardo Liceaga; ⁴Special Projects Unit, Asociación Mexicana para el Estudio Multidisciplinario del Síndrome Metabólico A.C., Instituto Mexicano del Seguro Social. Mexico City, Mexico

Abstract

The discovery and synthesis of insulin have been vital in the study and treatment of diabetes mellitus. From the studies carried by Dr. Nicolae C. Paulescu in 1921 and descriptions of the pancrein, before those published by Banting and Macleod, the Nobel Prize winners in 1923, more metabolic and non-metabolic actions have been discovered and that are fundamental for life, growth, and development of different organs and systems. Diverse studies in animal models have shown the participation in the development of the central nervous system, regeneration, neuronal apoptosis, and synaptic transmission, as well as the effects of its dysregulation in the pathophysiology of diseases such as dementia. Different researchers have demonstrated the synthesis of insulin at the brain, the mechanisms through which the blood-brain barrier crosses and how it regulates non-metabolic systems linked with the neuromodulation. This document to integrate these findings in the cerebral insulin circuit and the translation in clinical practice.

Key words: Alzheimer's. Brain. Dementia. Insulin.

Resumen

El descubrimiento y la síntesis de la insulina ha sido vitales en el estudio y el tratamiento de la diabetes mellitus. Desde los estudios realizados por el Dr. Nicolae C. Paulescu en 1921 y sus descripciones de la pancreína, antes de los publicados por Banting y Macleod, galardonados con el Premio Nobel en 1923, se han descubierto cada vez más acciones metabólicas y no metabólicas fundamentales para la vida, el crecimiento y el desarrollo de diferentes órganos y sistemas. En la actualidad, el estudio de esta hormona se nutre con más evidencia científica de su utilidad en blancos terapéuticos no metabólicos. Diversos estudios en modelos animales han demostrado su participación en el desarrollo del sistema nervioso central, la regeneración, la apoptosis neuronal y la transmisión sináptica, así como los efectos de su disregulación en la fisiopatología de enfermedades como la demencia. En la actualidad, diferentes investigadores han demostrado la síntesis de insulina en el cerebro, los mecanismos por los cuales atraviesa la barrera hematoencefálica y cómo regula sistemas no metabólicos ligados con la neuromodulación. Este documento trata de integrar estos hallazgos en un sistema insulínérgico cerebral y su posible traducción en la práctica clínica.

Palabras clave: Alzheimer. Cerebro. Demencia. Insulina.

Correspondence:

*Martín de J. Sánchez-Zúñiga

Avda. México Xochimilco, 289

Col. Arenal de Guadalupe. Del. Tlalpan

C.P. 14389, Ciudad de México, México

E-mail: mjsanchez@inr.gob.mx

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“Life evolution cannot be understood without insulin.”

Martín de Jesús Sánchez Zúñiga, 2018

Introduction

For many years, the concept that insulin did not cross the blood-brain barrier, or that it was not synthesized in brain tissue, prevailed. The first reports by Margolis and Altzuler demonstrated the existence of insulin in cerebrospinal fluid in murine and canine models, although at that time, they failed to find a linear constant or any correlation with plasma insulin levels. Subsequent investigations by Banks et al. demonstrated an insulin transport saturable mechanism that allows crossing the blood-brain barrier and that is independent of plasma glucose levels (most insulin crosses the blood-brain barrier in normoglycemia conditions)¹⁻⁴. Subsequent research has allowed demonstrating that insulin not only crosses the blood-brain barrier but that it is also synthesized in neuronal groups' specific regions and that it also has non-metabolic signaling functions.

This documents compile in detail the scientific evidence and propose the existence of a brain insulinergetic circuit, which is essential to the development of the central nervous system, and that its alterations can be an important part of the pathophysiology of disorders such as Alzheimer's disease⁵⁻⁷.

Brain insulin

Research by Dorn et al.⁸ demonstrated the presence of C-peptide and proinsulin in different areas of the brain, mainly concentrated in the hypothalamus. Studies by Zhao et al.⁹, labeling proinsulin 1 messenger RNA, have shown that expression predominance is found in the hippocampus, the olfactory bulb, the piriform cortex, and cerebral cortex Purkinje cells. Other studies have demonstrated that only a subset of neurons are responsible for insulin synthesis, mainly in the hippocampus¹⁰⁻¹³.

The insulin receptor (IR) is not uniformly distributed throughout the brain. The first investigations on the presence of IR in brain tissue carried out with radiolabels in different animal models showed that IR concentration is restricted only to some special sites, such as the circumventricular regions, medial hypothalamus, medial paravaginal regions, choroid plexus, and some peripheral nervous system regions¹⁴.

Subsequent studies with IR messenger RNA showed that the areas with the highest density are

distributed in regions of the hypothalamus, the cerebellum, olfactory bulb granular cells, the dentate gyrus, pyramidal cells, the piriform cortex, the hippocampus, the choroid plexus, and the arcuate nucleus of the hypothalamus. One of the main characteristics of IR distribution is that it is not directly related to cell density or to a larger amount of blood flow but it is abundant in regions with high dendrite density and synapsis, and it is therefore possible that this relationship plays an important role in neuronal activity, a phenomenon that is supported by the findings of high content of the IRSp58 and IRSp53 fractions of insulin receptor substrate (IRS), as well as other substrates similar to phosphatidylinositol 3 kinase-type effectors in synapses of the cerebellum, the cerebral cortex, and hippocampal neurons¹⁵⁻²¹.

IR is a protein of the kinase receptors family, and although both IRs (cerebral and peripheral) behave with the same pharmacology and kinetics, there are differences in molecular size, antigenicity, and carbohydrate composition, as well as in insulin-mediated regulation. One of the main differences is the type of response to the amount of insulin: while peripheral receptors respond with downregulation (with internalization and degradation), brain receptors remain constant.

IR embryonic development and distribution at specific sites of the brain are also related to the effects of cerebral growth, modulation, and development. Findings have shown that IR density at fetal stage is different from that of adult stage. In postmortem studies of human fetuses, and mainly in murine models, IR density has been observed to decrease with age, although this appears to be limited to the olfactory bulb; in addition, modifications have been found in alpha subunits molecular size²²⁻²⁹.

Insulin and other molecules, such as insulin-like growth factor-1, play an important role in neurons and glial cells signaling and energy metabolism. IR activation mediates molecular processes, the mitogen-activated protein kinase (MAP) kinase pathway, and the PI3k pathway, which, among other actions, inhibit apoptosis and promote growth, cell survival, gene expression, cytoskeleton assembly, synapsis formation, nerve transmission, and neuronal plasticity. The MAPK pathway mainly fulfills functions of signaling and gene transcription mechanisms activation, thus promoting neuronal growth and repair. PI3k pathway modulation participates in neurons by regulating tau protein phosphorylation/de-phosphorylation, a mechanism that is

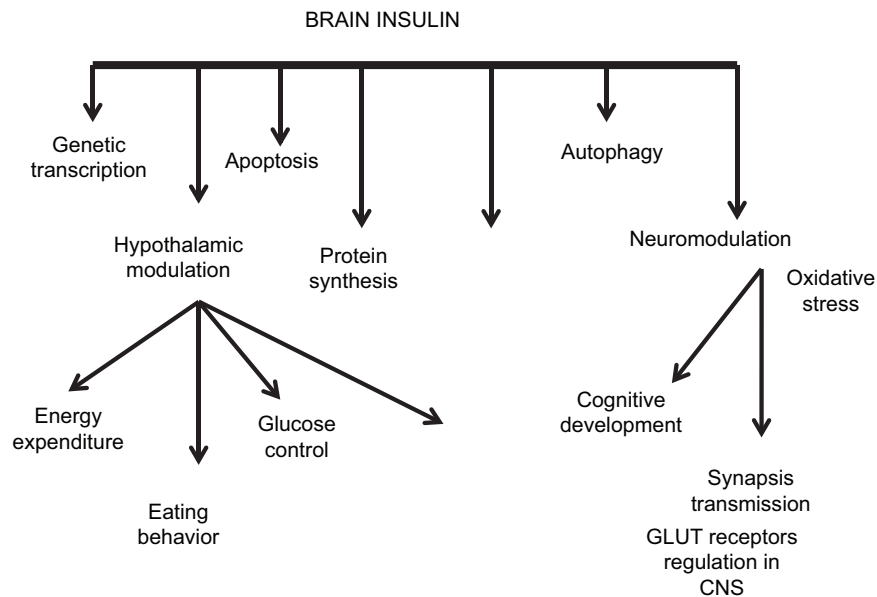


Figure 1. Insulin actions in the brain.

Table 1. Glucose transporters in the brain

GLUT isoform	Localization	Cell group	Regulation
GLUT 1	Ubiquitous and abundant	Glial cells and endothelium	Hypoglycemia and insulin
GLUT 2	Limited to hypothalamus	Neurons, glia, tanocytes	
GLUT 3	Abundant in the cerebellum, cortex, hippocampus, and striatum	Neurons, glia and endothelium	
GLUT 4	Only in special areas of olfactory bulb, hippocampus (dentate gyrus), cerebellum, and hypothalamus	Neurons and glia	Glucose and insulin
GLUT 8	Limited to hypothalamus, cerebellum, dentate gyrus, amygdala, and primary olfactory cortex	Neurons: proximal dendrites and proximal bodies	Glucose

GLUT: Glucose transporters

dependent on glycogen synthase kinase beta (GSK3- β) isoform activity regulation³⁰⁻³³ (Fig. 1).

Both metabolic and non-metabolic actions of brain insulin interaction with its receptor are a fundamental part in the regulation of the energy-related effects derived from glucose uptake and metabolism in neuronal and glial cells. These mechanisms mainly depend on insulin regulation on its GLUT transporters (hexose-facilitated diffusion transporters), out of which GLUT 1 and 3 are the most abundant in the cerebellum, hippocampus, cortex, hypothalamus, olfactory bulb, dentate gyrus, amygdala, and primary olfactory cortex, unlike GLUT 4 and 8, which are found in smaller numbers and limited to some neuronal groups and glial cells, particularly distributed

in the apical and proximal regions of cell bodies³⁴⁻³⁸ (Table 1).

GLUT-1 is the most widely distributed glucose transporters (GLUTs) in the human being; it is highly expressed in fetal tissues, such as erythrocytes, endothelial cells, nerve cells, the placenta, lymphocytes, the kidney, the retina, and adipose tissue. It has high affinity for glucose, and thus, it is able to constantly transport glucose into the cell regardless of the amount of plasma insulin and glucose and, therefore, it is of great importance in brain tissue, where its expression is constantly maintained. One of the most important characteristics is that GLUT 1 can act as transporter for other molecules, such as galactose, mannose, and glucosamine. There are two of GLUT 1 isoforms: the

55-kDa isoform is distributed mainly in endothelial cells of the blood-brain barrier, the neuronal membrane, and erythrocytes, and the second isoform, of lower molecular weight, is almost exclusive to glial cells. Diseases deriving from GLUT 1 alterations or deficiency occur as severe functional disturbances of the central nervous system, such as GLUT 1 deficiency syndrome, which is characterized by seizures, failure to thrive, complex movement disorder, and electroencephalographic changes in fasting conditions. Magnetic resonance imaging studies of these patients show a severe decrease in glucose uptake at the cerebral cortex³⁹⁻⁴¹.

GLUT 3 is also a high-affinity GLUTs, which was discovered mainly in brain tissue. Its distribution is limited in fetal and adult tissue to myocardial and skeletal muscle, to the liver, placenta, and brain tissue. Its main characteristic is that it is a GLUT 1 coaggregate, since, similarly, it has the function of constant glucose transport regardless of plasma glucose and insulin concentrations. Alterations in the expression of this transporter or mutations in its gene (SLC2A3, located on chromosome 12) have been shown to be associated with severe metabolic alterations at neonatal stage, psychomotor retardation, and intrauterine growth restriction. Other studies have demonstrated mutations in tumor cells and increased metastatic capacity, such as in testicular tumor cell lines. Alterations in this transporter's gene (larger number of copies) are also associated with Huntington's disease symptoms earlier onset⁴²⁻⁴⁶.

GLUT 8 shares high affinity for glucose with GLUT 3. It has been found predominantly in testicular cells, blast cells, the cerebellum, and hippocampus, and to a lesser extent in the spleen, prostate, liver, heart, and skeletal muscle. Glucose transport capacity is also independent of the amount of plasma glucose and is directly regulated by insulinergetic stimulus. So far, overexpression of the gene that encodes it (SLC2A8) has been demonstrated in Alzheimer's disease^{47,48}.

Proposal of the brain insulinergetic circuit

According to the description of scientific evidence, the existence of a brain insulinergetic circuit can be established, at least theoretically. It can be described, according to its kinetics, with the following important points (Fig. 2):

- Plasma insulin crosses the blood-brain barrier through a saturable pore system between endothelial cells (Virchow-Robin spaces) and choroid plexuses (paracrine effect traditional model).

- Insulin is also synthesized in cell groups of specific areas of the brain, the frontal cortex, the olfactory bulb, the cerebellum, the hippocampus and Purkinje cells, and interacts with its receptor via an autocrine pathway (autocrine effect non-traditional model).
- Brain insulin, from whichever origin, interacts with its receptor, which has a distribution density in specific sites in the brain, such as the circumventricular regions, medial hypothalamus, medial paravaginal regions, the choroid plexus, olfactory bulb, dentate gyrus, pyramidal cells, arcuate nucleus of hypothalamus, and some peripheral nervous system regions.
- Insulin action with its receptor, through tyrosine residues phosphorylation, triggers signaling mainly in two pathways: the MAPK pathway, which is mainly responsible for signaling, translation and gene signaling, and the phosphoinositide-3-kinase-protein kinase B/Akt (PKB/Akt) pathway, which is responsible for metabolic and secondary non-metabolic signaling actions.
- PKB/Akt pathway phosphorylation and activation is responsible for the regulation and control of kinases such as GSK3, which among its secondary activities, regulates tau protein phosphorylation/de-phosphorylation⁴⁹.
- PKB/Akt-mediated signaling and regulation also regulates AS160 (160 kDa Akt substrate) and Rab (monomeric GTPase of the Rab subfamily of Ras-related proteins) activity, which are responsible for activation and translocation of the GLUTs (GLUT 1, 3, 4, and 8) that are distributed in specific sites of the brain.
- The high sensitivity of specific GLUTs, such as 1 and 3, allows constant glucose input to the brain (regardless of plasma glucose and insulin concentrations), which maintains a constant energy source for mitochondrial, anti-inflammatory, anti-apoptotic, neuromodulation, growth, proliferation, synaptic signaling, oxidative stress, etc., functions.
- Endosomal insulinases are responsible for insulin degradation. IR is recycled for its new translocation to the plasma membrane. Under insulin resistance conditions, with a saturable system and hyperinsulinemia (type 2 diabetes and metabolic syndrome), IR is transported to lysosomes for its degradation, thus downregulating its availability, which is a mechanism that plays an important role in the resistance to the action of insulin⁵⁰.

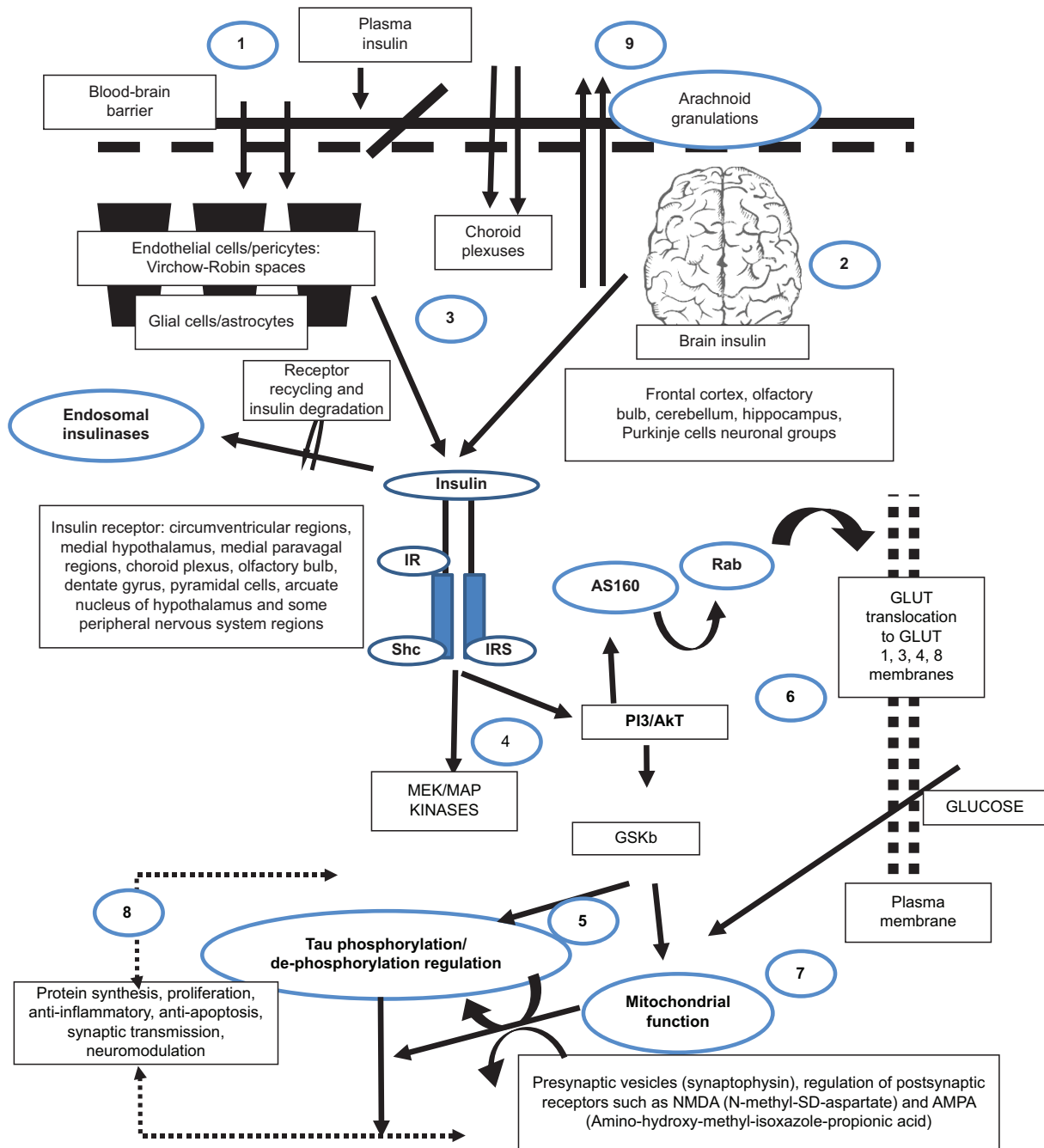


Figure 2. Brain insulinergic circuit (see text for explanation). AMPA: amino-hydroxy-methyl-isoxazole-propionic acid, GLUT: glucose transporters, GSKb: glycogen synthase kinase 3b, MEK/MAP: mitogen-activated kinase proteins complex, NMDA: N-methyl-D-aspartate, PI3/AKT: phosphatidylinositol 3-kinase complex, IR: insulin receptor, Shc: type 1 transducer protein, IRS: insulin receptor substrate.

Pathophysiological integration

The term type 3 diabetes mellitus, recently coined by several researchers, could be explained by the insulin-mediated signaling dysregulation mechanism in this brain insulinergic circuit, which translates into hyperphosphorylation of essential proteins in synaptic

neurotransmission, which clinically manifests as cognitive impairment.

According to histopathological findings in animal models, *in vivo* human brains and postmortem brains, there are signs supporting that insulin signaling alterations in the brain participate in the appearance of the main pathological phenomena observed in Alzheimer's

disease, such as beta-amyloid (BA) deposition, tau protein hyperphosphorylation, inflammation and increased plasma, and cerebrospinal fluid biomarkers. Insulin resistance is an essential part of these mechanisms, either due to IR downregulation or due to insulin-degrading enzymes (insulinases) supersaturation, which share a secondary mechanism of action in the elimination of the BA peptides that are generated by the action of specific secretases that degrade these peptides.

IR blockage facilitates phosphorylation of IRS-1-4 binding sites serine residues (usually from tyrosine residues phosphorylation). This imbalance blocks the signaling of the two main pathways of response to insulin action. On one hand, the one is mediated by MAPK, in which among other actions regulate the activity of other kinases, proteins, and proteinases that are responsible for the regulation and elimination of toxic products, including the clearance of BA peptides. On the other hand, by avoiding PI3k activation, the negative regulation of kinases such as GSK3b and tau-tubulin kinase (TauK) and KDC2 and 5 (cyclin-like kinases 2 and 5), which normally control tau protein phosphorylation, is lost.

This imbalance in phosphorylation/de-phosphorylation regulation facilitates tau aggregation in neurofibrillary clusters or tangles (formed by hyperphosphorylated tau protein), thus altering the microtubular structure and blocking axonal and synaptic transmission, which limits neurotransmitters and presynaptic vesicles, such as synaptophysin, availability, BA accumulation, and downregulation of postsynaptic receptors such as N-methyl-D-aspartate and amino-hydroxy-methyl-isoxazole-propionic acid. In addition, insulin signaling blockade limits transmembrane GLUTs expression, which limits glucose input for the mitochondrial metabolism and energy function that generates higher oxidative stress, inflammation, and apoptosis⁵¹⁻⁵⁷.

Conclusions

So far, there is scientific evidence demonstrating that insulin plays a preponderant role in neuromodulation and not only since embryogenesis by promoting central nervous system growth and development but also as an important neuromodulator of non-metabolic responses in adulthood, mainly associated with synaptic transmission, cerebral apoptosis, neuronal regeneration, inflammation, oxidative stress, etc. There is also increasing evidence that this hormone can be synthesized in specific groups of neuronal

cells, as well as on its ability to cross the blood-brain barrier, and that when interacting with its receptor, which is distributed only in some special areas of the brain, it modulates a series of non-metabolic responses that are involved in synaptic transmission proper functioning. Probably the clearest example of this dysfunction is tau protein phosphorylation/de-phosphorylation pathway dysregulation and the formation of neurofibrillary tangles, as one of the main pathophysiological findings in Alzheimer's disease⁵⁸⁻⁶¹.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical disclosure

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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