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Review Article

A review on insulin presence and function in brain

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ABSTRACT

Hormones have major role in maintaining the homeostasis of the body and mental functions. One of the crucial hormones that act to regulate the metabolism and growth is insulin. Insulin activity in the periphery has been the subject of study since long time ago, though, beginning to understand the central activity of insulin is rather recent and because of complexity of actions and interference with neurodegenerative diseases such as Alzheimer's and Parkinson's and mood disorders, like anxiety and depression, it is considered very crucial hormone in the maintenance of the mental health. This mini-review will discuss briefly the recent main aspects of insulin transfer to the brain, receptor and mediators, signaling pathways with particular attention to neural system and its role in cognitive and emotional processing in brain. Insulin is an endocrine hormone with receptor distribution in different parts of brain and has role in various neural functions such as; growth factor, modulating learning or memory, mood, neural growth and survival, also controlling neurotransmitters functions in different brain regions. Insulin regulates metabolic homeostasis in brain through complex routes, which inevitably makes it involved with some neurodegenerative or affective disorders, that raises its importance for more serious studies.

Keywords: Insulin, Brain, Metabolism, Cognition, Neurodegenerative, Depression

INTRODUCTION

In humans and most of the lower level creatures, except the primitive shapes of livings, the balance in interaction between the hormones and nervous system renders what is called balanced or normal state of mind. Since, physiologically, there are several groups of hormones releasing and acting to produce the homeostatic body function, thus the balance in releasing each of them would be very crucial in vitality. There is a large amount of close interaction between brain and almost all groups of hormones in the body. Even the function of the neurons in the nervous system is orchestrated by local chemicals. It is the physiology of the vital being which dictates the balanced release and actions of hormones to regulate the nervous system functions in ways such as controlling the metabolism and level of functions of the neurons, directly or indirectly. Brain is equipped with almost all hormone receptors that are normally produced and released in the periphery; from the digestion system to thyroid, gonadal and adrenal hormones.

Almost all the body hormones have effect on brain activity and behavior, though, in this review, we will confine our overview to the latest findings related to insulin, as a hormone with vast peripheral metabolic functions and crucial effects on cognition and mood. We focus our view on insulin role in regulation of cognitive function and mood disorders. Insulin was chosen, because the insulin deficiency-related disease, diabetes, and its subsequent cognitive disorders, like dementia and Alzheimer's disease, are becoming one of the major problems in today's modern world.

INSULIN AND NERVOUS SYSTEM

Insulin is released from the beta-cells of pancreas into the blood and since it is rarely bound to the plasma proteins, it has a short half-life of 6 min. Insulin has critical role in glucose, fat and protein metabolism in the body. Brain also needs insulin for coordination of metabolism and cognitive process.[1] Until late 1970, brain was considered as insulin-insensitive organ. At that time, it was demonstrated that intra-cerebro-ventricular (ICV) injection of insulin reduced feeding behavior in experimental animals.[2] The metabolic actions of insulin in the brain is mostly related to feeding, body weight,[2] and hepatic metabolism. It acts on the hypothalamic nuclei to control feeding and studies have shown that this ability is dramatically reduced in obese rats or those with high fat diet.[1] Other functions of insulin in central nervous system (CNS) are: controlling neurotransmitter release, neuronal growth, formation of tubulin and cellular survival.[3] Recent studies indicate that people with diabetes type II or insulin résistance are more at risk of Alzheimer's disease and dementia than other people, which suggests the action of insulin on the hippocampus and cerebral cortex.[4] Previous studies have shown that mothers with gestational diabetes provide an inappropriate intrauterine environment for fetus growth of different organs including the nervous system.[5]

INSULIN ORIGINS IN THE BRAIN

There is solid evidence that insulin can pass through the blood brain barrier and cerebro-spinal fluid (CSF) to reach the brain interstitial fluid (BISF). Although the concentration of insulin in CSF is often lower than plasma, it is mostly higher in BISF than CSF, so this suggests that insulin passes through the blood–brain barrier (BBB) (in addition to cerebo-spinal barrier) via other pathways. In addition to the regions of the brain that lack the BBB, like median eminence of hypothalamic area, insulin receptors on the luminal membrane of the microvascular brain endothelial cells can directly transit insulin through the endothelial cells, which are bound by tight junctions and adherent junctions (in contrast to blood-CSF barrier that has fenestrated endothelial lining cells). Afterward, the insulin/receptor complex is internalized by lipid raft-mediated endocytosis process and quickly is moved toward the basal membrane, it releases there and can interact with astrocytes or enter BISF and interact with neurons and glia.[1,6] Another factor that facilitates the transport of insulin into the brain is the neurovascular coupling mechanism. Increase in neural activity produce local vasodilation and neurovascular coupling, which facilitates transferring of some hormones, such as IGF-I across the brain endothelial cell barrier.[7] That might be the same auxiliary route for insulin too, since regional increase in the cerebral blood flow have been seen during the fMRI after having a high glucose meal and raise in the plasma insulin subsequent to that.[1] Besides to the transferring of the circulating plasma insulin into brain, there is some evidence that certain brain regions might produce insulin themselves.[1,8] However, some neuronal areas in the brain do produce insulin-like peptides, such as those belong to Relaxin hormone family, and insulin like growth hormones (factors), IGF I, II.[9]

INSULIN RECEPTOR AND SUBSTRATE PROTEINS

Insulin and related IGF-I and II act on two highly related tyrosine kinase receptors, IR and IGF-IR.[10] IGF-IR has higher affinity for IGF-I than II and 500-folds less affinity for insulin. In cells that express both IR and IGF-IR, a hybrid receptor may form by each half, with unknown physiological role.[11] However, it is very likely that the heterodimere is more responsive to IGF-I than to insulin. This heterodimerization also demonstrate considerable cross-talk between IR and IGF-IR in various regions of the brain.[10] In rodents the greatest density of insulin receptor, IR, is in the olfactory bulb and then in the hypothalamus, hippocampus, cortex, cerebellum,[1] amygdala and septum.[12] There are two receptor isoforms for insulin, A and B. In adults, type B is prominent in the periphery, while type A is more found in the brain.[13] Insulin receptor and IGF-I acting intracellularly through a substrate, insulin receptor substrate, IRSs, with three subtypes present in the brain, IRS-1, IRS-2 and IRS-4, each abundant in different regions and with IRS-1,2 both display similar and distinct functions. It seems like that IRS-1 is more engaged in brain and body growth, while IRS-2 is more related to brain development.[10] For metabolic functions of IR in the ventral hypothalamic area IRS-2 is more likely to be involved, because of its higher distribution in the area.[14] Also, IRS-4 has partly similar functions to IRS-1 and 2.[10]

INSULIN INTRACELLULAR SIGNALING AND PROTECTION OF NEURAL SURVIVAL

Binding insulin to IR leads to two signaling pathways: the main route for intracellular signaling of insulin is IRS-1activation or phosphoinositide 3-kinase or protein kinase B (Akt), PI3K/Akt, pathway. Subsequently, other protein targets in this way are involved including, mTORC1, GSK3β, and FoxO family of transcription factors. mTORC1-mediated protein synthesis is important in neural plasticity and autophagy, which is a mechanism in neurons to destroy misfolded proteins and damaged organelles. GSK3β has a role in neuronal polarity, neural progenitor cell proliferation, and neuroplasticity.[10] Insulin stimulates phosphorylation of GSK3β and in this way reduces its enzymatic activity to phosphorylate tau proteins. Knocking out IR or IRS-2 would increase phosphorylation of tau protein by GSK3β and leads to accumulation of neurofibrillary tangles containing phosphorylated tau. FoxO prevents activation of two pro-apoptotic proteins in the cell.[15] Therefore, the IP3K pathway demonstrates that insulin action through IR has neuroprotective role in the brain. Specific inhibition of GSK3β by insulin proves its neural protection against

development of neurodegenerative process in the brain that is well known consequence of diabetes type II and insulin resistance.

The second pathway for insulin intracellular signaling is via binding an adaptor protein SHC to the tyrosine kinase binding domain. SHC binds to "growth factor receptor binding protein 2 (GRB2)" and a "guanine exchange factor named son of sevenless (SOS)". GRB2 or SOS assists with activation of Ras, a member of small GTPase family proteins and thereafter a cascade of signaling proteins are activated and followed including Raf, MAP2K or MEK and "extracellular signal-regulated kinase 1 and 2, ERK1/2", which in turn they activate the nuclear transcription factors.[3] Grb2-SOS-Ras-MAPK cascade, has important role in cell proliferation, differentiation and gene expression, which in the brain leads to neural survival and normal physiological function.[10] Cross-talk between PI3K/Akt and Ras/MAPK pathways may lead to phosphorylation of Raf by PI3K/Akt and therefore, downstream activation of ERK1/2 is inhibited. This would be of benefit for some neural cells, like in cerebellum, in which activation of ERK1/2 renders to cell death. In this type of neurons, insulin (and IGF-1) apparently acts through IGF-1 receptor and through PI3K/PKB/Akt pathway block ERK1/2 activation and therefore, promote cell survival.[3]

INSULIN AND COGNITION

There are many evidences indicating the insulin function as a cognitive and behavior modulator in the brain.[16] The location of insulin receptor in the brain, like insulin medial temporal lobe in human, supports the idea of having important role in learning and memory process. Also, in human and rat acute insulin administration displayed improvement in learning ability and memory.[12] Expression of insulin receptors and probably insulin in the hippocampus and PI3K pathway, both have protective role in neuronal maintenance and strength of the neural plasticity in the hippocampus.[3] The association between insulin and cognitive activities is evident by knowing that the downstream signaling of insulin and IGF-I is markedly reduced in hippocampus and frontal cortex of patients with Alzheimer's, which indicates the brain is insulin resistant in these patients.[15] Also, mice receiving high lipid diet displayed reduced hippocampal-dependent spatial memory and lower dendritic spines and with less brain derived neurotrophic factor, BDNF in their hippocampus.[17,18] The relation between insulin and neurotrophines like BDNF nicely gets along with the role of insulin in synaptogenesis and synaptic remodeling.[12] Interestingly, in another study a single insulin injection induced reduction in the amount of Aβ amyloid levels in the brain of mice model of Alzheimer's with high lipid diet.[4] It was in 1996 that researchers found there is a relation between type II diabetes and dementia. Later studies supported this finding by more solid evidence relating type II diabetes with dementia and Alzheimer's.[12] Moreover, patients with Alzheimer's display reduced expression and function of IR, IGF-1receptor, and IRS-1 proteins in the brain, specifically in the hippocampus and hypothalamus, in addition to increased serine phosphorylation (normally is threonine) in IRS-1, which has inhibitory function.[10] They also demonstrate lower insulin in CSF related to plasma. Clinically, administration of nasal insulin can decrease the cognitive disabilities in these patients.

Because of close relation between cellular downstream signaling mechanisms of insulin/IR complex and Alzheimer's pathology, this disease is also called "type-3 diabetes".[12]

Insulin interacts with some neurotransmitter systems in relation to mental function. A study indicate that insulin can downregulate the expression of norepinephrine (NE) transporter NET in the locus coeruleus and in this way modulate NE pathways in the brain.[19] Likewise, interacts with cholinergic system in consolidation phase of memory in certain conditions.[20]

In addition, insulin regulates different types of neurotransmitter receptors in the brain and acts as a neuromodulator. Insulin is engaged in the hippocampal neural plasticity by regulating the transmission of N-methyl-d-aspartate (NMDA) receptors to the excitatory post-synapses in the hippocampus, therefore, an insulin-induced enhancement in long term potentiation in hippocampal neurons is developed, which has positive effect on learning and memory.[8,21] Likewise, by having regulatory effect on GABAergic transmission, it can control the activity of inhibitory synapses. Also, by down regulating the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, it affects memory consolidation.[10] It is more likely that insulin improves cognitive abilities by regulating between long term potentiation and depression of glutamate synapses in hippocampus and probably prefrontal cortex.

Furthermore, insulin can increase brain glucose metabolism in certain regions related to cognitive functions. These regions have specific glucose transporter GLUT4 and 8 distributions that acts under influence of insulin. In the rat brain GLUT4 transporters are distributed in the cerebellum, sensorimotor cortex, hippocampus, pituitary, and hypothalamus and GLUT8 mostly in the hippocampus and hypothalamus.[12] Interestingly, the reverse is also true; studies have shown that triggering the learning process and advancing memory also have induced increase in the insulin receptors and associated proteins in the brain.[12]

IRSp53 is another substrate protein for insulin receptor that is abundantly found in periphery and also several regions of the brain. Defects in expression of this protein are observed in variety of neurological disorders such as autism, schizophrenia and attention deficit/hyperactivity disorder. IRSp53 is densely located in the post synaptic density (PSD) of glutamatergic neurons. Its main function

is to regulate the density of NMDA receptor at the post synaptic locations. Knocking out or malfunctioning of IRSp53 leads to increase in the NMDA receptors and over production of LTP in hippocampus and poor functioning in the simple cognitive abilities. Studies have shown that even moderate reduction in IRSp53 has led to defects in formation of memory in mice.[22]

INSULIN AND STRESS AND COGNITION

It is well known that stress, particularly chronic stress, interferes with Hypothalamic-Pituitary- Adrenal axis (HPA axis) and changes the level of glucocorticoids (GCs) in the blood and its subsequent transfer to different regions in the brain as well as changing in the distribution of the glucocorticoids receptors (GR) in various regions, including hippocampus and prefrontal cortex. In the case of chronic stress, long acting of the higher levels of GCs in brain disturbs the learning and memory consolidation process and therefore, may lead to deficits in learning and memory as well as other cognitive and mood processes, like depression.[23,24] GCs also interfere with whole body metabolic function and in consequence, insulin /receptor system. Exposure to chronic stress is most likely accompanied by insulin resistance. Likewise, administration of glucocorticoids for long time highly increase the probability of hyperglycemia and hyperinsulinemia followed by insulin-resistance.[25] In case of brain insulin resistance, studies point to the activation of a "stress-activated protein kinase (SAPK)", named "c-jun-n terminal kinase, JNK", a member of MAPK family. JNK can inhibit IRS-1, by phosphorylating the protein at serine residues, and in this way, it blocks the signaling transduction once started by IR.

GCs are also able to end the ERK1/2 pathway in hippocampus and in this way interfere with cognitive and memory processing. GCs activate MAPkinase phosphatase-1 and terminate the pathway by deactivating ERK1/2.[26] Whether GCs can interfere with insulin action on hippocampus-based learning abilities is a possibility, since GCs can interfere with MAPK signaling pathway and insulin induced-MAPK pathway is one of them.

INSULIN AND MESOLIMBIC REWARD SYSTEM

Depression is the most common deficit that follows insulin-resistance or diabetes type-II. Depression is a mood disorder that occurs in result of mesolimbic reward circuit malfunction. The mesolimbic dopamine system mediates different aspects of reward processing and this is usually performed by release of dopamine from the ventral tegmental area (VTA), into ventral striatum nucleus accumbens, NAc that is the center of evaluation of reward in the brain.

Insulin receptors are distributed across the reward circuit that suggests a modulatory role for this hormone in motivational aspects of food intake.[27] IRs are expressed on VTA neurons and studies have demonstrated insulin signaling cause increase in the reuptake of dopamine by VTA.[28] Intra-cerebral injection of insulin or hyperinsulinemia cause increase in dopamine transporter, DAT, mRNA in the VTA area.[29] Up taking dopamine increases dopamine turnover and thus reduces its release in the destination regions, most importantly, NAc. Insulin acts opposite in relation to another catecholamine, norepinephrine (NE). Insulin downregulates the expression of NE transporter, NET, in the locus coeruleus, and by that it increases NE effect in synapses.[19] Another mechanism explaining insulin-induced inhibition on dopamine release comes from studies that demonstrated insulin can cause inhibition on VTA neurons pre- and postsynaptically. In postsynaptic case, insulin increases down regulation of AMPA receptors and therefore, produces LTP, which is based on PI3K/Akt/mTOR pathway. Presynaptically, a study beautifully showed that insulin binding to VTA neurons causes the release of endocannabinoids retrogradely to the presynaptic glutamate neuron that inhibits the glutamate release and induced LTP in postsynaptic dopamine VTA neurons.[30]

However, insulin action toward reducing the incentive feeding depends on the concentration of insulin in the VTA area. In cases of hyperinsulinemia, like feeding the mice with high fat-sweet food one hour prior to slicing its brain, has shown that induction of long-term depression by insulin is reduced.[30] Also, a study with human subjects has shown that administrating nasal insulin spray did not reduce the incentive aspects of food taking in insulin-resistance subjects, in opposite to healthy subjects.[27] Therefore, it seems that physiological levels of insulin is able to bring back the increased metabolism to homeostatic levels by inducing decrease in palatability through suppressing reward system.

There are other studies that provided new insights for better understanding the relation between insulin and mood disorders. There is a possible link between depression and mitochondrial dysfunction.[31] Mitochondrial malfunction might lead to changes in the levels of monoamine oxidase enzyme (MAO) and oxidative stress. Central insulin-resistance is usually associated with mitochondrial dysfunction, which leads to changes in the expression of mitochondrial enzymes MAO type A and B.[32] A study revealed the increase in levels of MAO was only restricted to NAc and dorsal striatum. *In vitro* studies have shown that insulin can directly down-regulate both MAO A and B in neurons but only MAO A in glial cells. Therefore, the outcome of reduction in insulin action in brain is up-regulation of MAO A and B, increased clearance of dopamine and thus reduction in dopamine signaling. Increase in MAO also degrades serotonin as well, which may increase the chance of mood disorders, such as anxiety and depression, following insulin dysfunction and insulin-resistance in brain.[33]

We can also look into the relation between central insulin function and mood from another angle. We know that insulin binding to its Tyrosine kinase receptor acts via PI3K-AKT and Ras/Raf/MEK/ERK1/2 signaling pathways in brain. Also, BDNF binding to its Tyrosine kinase receptor, TrkB, follows Ras/Raf//MEK/ERK1/2 and PI3K-AKT signaling pathways to regulate neurite elongation, branching and neural survival.[34] Since both BDNF and insulin act through the same structure family receptors and follow the same signaling route, which both ends with expressing proteins used for neural growth and survival, thus we may develop an assumption that there might be an interaction between them and dysfunction of one might affect the other. There are some strong evidence of reduced levels or functions of BDNF in brain, especially in hippocampus, of patients and animals with depressive-like behaviors, which usually result in decreased neural plasticity and degenerative changes in hippocampus morphology. These are the deteriorative changes that lead to depressed behavior associate with waned cognitive ability.[35-37]

CONCLUSION

Insulin, an endocrine hormone and central growth factor, is released from pancreas and passes through the blood brain barrier to act on its receptors distributed across the brain, not only regulates the metabolism through the central nuclei, most importantly hypothalamus and paraventricular area, also acts in other regions to modulate the learning, memory, mood, neural growth and survival, neural and glial oxidation by regulating mitochondrion enzyme synthesis and function and neural inflammation, also controls catecholaminergic, cholinergic, glutamatergic and GABAergic neurotransmitters and their receptors functions in various regions of the brain such as hippocampus, cerebellum, olfactory bulb, striatum, midbrain areas of VTA /substantia nigra and cortex. It is very interesting that insulin main goal in brain is to regulate metabolic homeostasis, similar to periphery; however, in order to accomplish this goal, it acts through very delicate and complex routes interacting with various systems and intracellular signaling molecules and pathways, which inevitably involves it with very serious neurodegenerative (Alzheimer's) or disastrous mood disorders (major depression).

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