Review

MOLECULAR METABOLISM

Insulin in the nervous system and the mind: Functions in metabolism, memory, and mood

Seung-Hwan Lee [1,2,5], Janice M. Zabolotny [1,5], Hu Huang [1,3], Hyon Lee [4], Young-Bum Kim [1,*]

ABSTRACT

Background: Insulin, a pleotrophic hormone, has diverse effects in the body. Recent work has highlighted the important role of insulin's action in the nervous system on glucose and energy homeostasis, memory, and mood.

Scope of review: Here we review experimental and clinical work that has broadened the understanding of insulin's diverse functions in the central and peripheral nervous systems, including glucose and body weight homeostasis, memory and mood, with particular emphasis on intranasal insulin.

Major conclusions: Implications for the treatment of obesity, type 2 diabetes, dementia, and mood disorders are discussed in the context of brain insulin action. Intranasal insulin may have potential in the treatment of central nervous system-related metabolic disorders.

Keywords Insulin; Intranasal insulin; Memory; Metabolism; Mood

1. INTRODUCTION

A fundamental metabolic action of insulin is to control blood glucose concentration by stimulating glucose transport into muscle and adipose tissue, and inhibiting hepatic glucose output [1]. It is now clear that the brain is recognized as an insulin-sensitive organ that is responsible for physiologic changes in altered metabolic disorders such as obesity and type 2 diabetes [2,3]. Insulin's actions are triggered by binding to its cell-surface receptor, which is present in virtually all mammalian cells [4]. In the brain, the insulin receptor is broadly expressed in regions including the hypothalamus, hippocampus, and cerebral cortex, all of which are involved in the metabolic control of insulin action, including feeding behavior, body weight homeostasis, neuronal development and cognitive function [3,5]. Insulin also plays important roles in neuronal circuitry formation, synaptic maintenance, neuronal survival, dendritic arborization, as well as learning and memory [6]. In this article, we review experimental and clinical studies that have demonstrated a new function of insulin in metabolism, memory, and mood. We also highlight emerging evidence that delivery of insulin to the central nervous system (CNS) via intranasal administration affects CNS-related metabolic disorders that are linked to impaired insulin action.

2. INSULIN ACTION IN THE BRAIN

2.1. Brain is an insulin-responsive organ

Crucial experimental evidence showing that the brain-specific deletion of the insulin receptor in mice leads to obesity, hyperphagia, and systemic insulin resistance clearly demonstrates the important function of brain insulin signaling in regulating metabolic homeostasis [7]. Emerging data also reveal that brain insulin signaling plays a pivotal role in regulating peripheral metabolism via the modulation of autonomic nervous system outflow to peripheral tissues [8,9]. For example, intracerebroventricular infusion of insulin in the murine brain suppresses hepatic glucose production (HGP) independent of circulating insulin and glucose levels, and these effects were abolished by inactivation of the insulin receptor in the brain [8]. Furthermore, activation of hypothalamic insulin signaling inhibited lipolysis and stimulated de novo lipogenesis by dampening sympathetic nervous system outflow to adipose tissue, whereas mice lacking the neuronal insulin receptor showed unrestrained lipolysis and decreased de novo lipogenesis in adipose tissue, highlighting the functional link of insulin signaling in the axis of the brain and periphery [9]. Thus, these peripheral metabolic responses driven by brain insulin signaling could be a decisive indicator for assessing brain insulin resistant states. Proving this issue in humans, however, is technically beyond the scope of

[1]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, 330 Brookline Ave., Boston, MA 02216, USA [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, South Korea [3]Human Performance Laboratory, Department of Kinesiology and Physiology, East Carolina Diabetes and Obesity Institute, East Carolina University, 115 Heart Dr., Greenville, NC 27858, USA [4]Department of Neurology, Neuroscience Research Institute, Gachon University Gil Medical Center, 21 Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, South Korea

[5] Seung-Hwan Lee and Janice M. Zabolotny contributed equally to this work.

*Corresponding author. Beth Israel Deaconess Medical Center, 330 Brookline Ave., CLS-745, Boston, MA 02216, USA. Tel.: +1 617 735 3216; fax: +1 617 735 3323.

E-mails: hwanx2@catholic.ac.kr (S.-H. Lee), jzabolot@bidmc.harvard.edu (J.M. Zabolotny), huangh@ecu.edu (H. Huang), hyonlee@gilhospital.com (H. Lee), ykim2@bidmc.harvard.edu (Y.-B. Kim).

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reach. On the other hand, by applying insulin intranasally to the human brain, the impacts of central insulin action on whole body metabolism can be evaluated.

In addition to these metabolic roles of the brain insulin receptor, a recent study further demonstrated that insulin resistance in brain induces dopaminergic dysfunction leading to anxiety and behavioral disorders [10], indicating a new role for insulin signaling in neuronal regulation. Along with this, a study with mice lacking brain insulin receptor substrate 2 (IRS2), one of the major downstream signaling pathways for the insulin receptor, suggests a potential role of IRS2 in the regulation of hippocampal synaptic function and plasticity in mice, which could be mediated via the N-methyl-D-aspartate (NMDA) receptor and the phosphoinositide 3-kinase (PI3K) signaling pathway [11]. It is therefore likely that defective insulin signaling in the brain is one of the key features in the pathogenesis of insulin resistance that is found in obesity, type 2 diabetes, memory impairement, cognitive dysfunction, and mood disorders (Table 1) [3,12].

2.2. Transport of endogenous insulin across the blood brain barrier

To gain access to its receptor in the CNS, insulin produced by pancreatic beta-cells is transported across the blood brain barrier (BBB) [13,14]. The BBB is composed of specialized capillary endothelial cells that are interconnected with tight junctions, which are impermeable to toxins, bacteria, viruses, and most substances in the blood (cells/proteins). The cells composing the BBB are unique in that the cell membranes are exposed to the bloodstream and the CNS, allowing integration of signals from the periphery and the brain [6]. The transport of insulin from the bloodstream across the BBB is

Table 1 — Animal models of CNS insulin receptor deficiency.

CNS function	IR deficient model	Phenotype	Observations	Refs
Metabolism	Mouse IR knockout in nestin expressing neurons	Weight	Increased food intake in female NIRKO (brain-specific insulin receptor deficient) mice. Development of diet-sensitive obesity with increases in body fat and mild insulin resistance in both male and female mice.	[7]
	Rat hypothalamic IR antisense knockdown	Weight	Rapid onset of hyperphagia, increased fat mass, and impaired hepatic insulin action. No significant change in body weight.	[38]
	Rat hypothalamic IR antisense knockdown	Weight	Increased body weight and fat mass. No changes in glucose tolerance and glucose—stimulated insulin release.	[39]
	Mouse IR knockout in tyrosine hydroxylase expressing neurons	Weight	Increased body weight, fat mass, and hyperphagia. Altered response to cocaine under food-restricted conditions.	[138]
	Rat hypothalamic IR antisense knockdown	Glucose homeostasis	Impaired ability of circulating insulin to inhibit glucose production.	[8]
	Mouse IR knockout in nestin expressing neurons	Glucose homeostasis	Defective counterregulatory response to hypoglycemia	[139]
	Mouse IR knockout in POMC expressing neurons	Glucose homeostasis	Unaltered energy and glucose homeostasis.	[41]
	Mouse IR knockout in AgRP expressing neurons	Glucose homeostasis	Unaltered energy homeostasis. Impaired insulin-induced suppression of hepatic glucose production. Reduced insulin-stimulated IL-6 expression in the liver.	[41]
	Knockin IRs in AgRP or POMC neuron on hypothalamic deficiency of insulin receptors (L1 mouse)	Glucose homeostasis	Restoration of insulin action in AgRP neurons and normalized insulin suppression of HGP. Restoration of insulin action in POMC neurons and increased HGP. Increased energy expenditure and locomotor activity by POMC-specific IR knock-in.	[50]
	Mouse IR knockout in nestin expressing neurons	Glucose homeostasis	Glycemia-dependent impairment in the sympathoadrenal response to hypoglycemia due to deletion of IR in the brain.	[140]
	Rat VMH IR antisense knockdown	Glucose homeostasis	Glucose intolerance and islet dysfunction. No effect on weight.	[40]
	Mouse IR knockout in nestin expressing neurons	Lipid homeostasis	Unrepressed lipolysis and reduced de novo lipogenesis in white adipose tissue.	[9]
	Mouse IR knockout in nestin expressing neurons	Hyperthermia	Defective IGF-1 mediated hyperthermic response.	[141]
Memory	Mouse IR knockout in nestin expressing neurons	Neuronal function	No alteration in neuronal proliferation/survival, memory, or basal brain glucose metabolism.	[114]
	Mouse IR kinase +/−	Behavioral function	Impaired recognition of familiarized objects; poor performance on both short-term (1 h) and long-term (24 h) memory tests in IR kinase +/− mice.	[117]
	Mouse IR knockout in nestin expressing neurons in Tg2676 AD mouse model	Neuronal function	Protection from premature death in the presence of decreased Aβ accumulation specifically in the hippocampus formation in nIGF-1R(−/−)Tg2576 mice with no influence on lethality of Tg2576 mice.	[115]
	Mouse IR knockout in nestin expressing neurons in Tg2676 AD mouse model	Neuronal function	Decreased Aβ burden without rescue from premature mortality of Tg2576 mice.	[142]
Mood	Rat hypothalamic IR antisense knockdown	Behavioral function	Increase in immobility time with corresponding decrease in active behaviors and increases in anxiety-like behaviors	[134]
	Mouse IR knockout in nestin expressing neurons	Behavioral function	Development of age-related anxiety and depression-like behavioral changes that were reversed with antidepressant treatment	[10]

AD, Alzheimer's disease; AgRP, agouti-related peptide; CNS, central nervous system; HGP, hepatic glucose production; IGF-1, insulin-like growth factor-1; IR, insulin receptor; POMC, proopiomelanocortin; VMH, ventromedial hypothalamus.

