MINI-REVIEW

BRAIN INSULIN RECEPTORS: EFFECTS ON FOOD INTAKE, LEARNING AND MEMORY

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ABSTRACT

Insulin and insulin receptors have been demonstrated in mammalian brain but until recently their function remained illusive. Insulin receptors are predominantly expressed in the olfactory bulbs, hypothalamus, and hippocampus. Recent studies have shown that insulin acts in the control of diverse brain functions such as neuronal survival, regulation of energy homeostasis, reproduction, food intake and body weight and life-span and as well learning and memory. Hyperinsulinaemia along with peripheral euglycaemia was shown to reduce food intake and to improve learning and memory. The present review summarizes recent data on the involvement of brain insulin receptors on the control of food intake and learning and memory. Resistance in brain insulin receptor signalling has been suggested to underline conditions as obesity and the cognitive dysfunctions in patients with Alzheimer's disease.

Key words: Alzheimer's disease, cognition, cognitive dysfunction, dementia, insulin resistance, obesity

INTRODUCTION

Insulin is a phylogenetically ancient hormone, found in some form in organisms ranging from molluscs to mammals (1). In mammals, insulin is a very important hormone, which in general terms promotes anabolic processes and inhibits catabolic processes. Specifically, it increases the rate of synthesis of glycogen, fatty acids and protein, and inhibits the breakdown of protein and glycogen. A vital action of the hormone is to stimulate cells such as liver, muscle and fat to remove glucose, some other sugars and amino acids from the blood. Insulin regulates glucose homeostasis at many sites, reducing hepatic glucose output (via decreased gluconeogenesis and glycogenolysis) and increasing the rate of glucose uptake, primarily into striated muscle and adipose tissue. Insulin regulates the uptake of glucose from the circulation by inducing the translocation of glucose transporters from the cytoplasm towards the plasma membrane. The glucose, taken by the transporters, is then stored or directly used as fuel (2). Insulin also profoundly affects lipid metabolism, increasing lipid synthesis in liver and fat cells, and attenuating fatty acid release from triglycerides in fat and muscle.

In humans the insulin gene is located in the short arm of chromosome 11. The insulin gene is expressed in the β cells of the islets of Langerhans in the pancreas as a precursor protein, proinsulin, of 104 to 109 amino acids depending on the species. Insulin is a small protein with a molecular weight of about 6000 Da secreted by exocytosis in response to increased circulating levels of glucose and amino acids after a meal. Insulin exerts its effects through binding to specific insulin receptors, expressed in most tissues of the body, including classic insulin-sensitive tissues (liver, muscle, and fat), as well as "insulin-insensitive" tissue, such as red blood cells and the neuronal tissue of the CNS (3).

The insulin receptor belongs to tyrosine kinase family and is a transmembrane tetramer composed of two alpha subunits (Mr 135,000) and two beta subunits (Mr 95,000) linked by disulphide bonds. The alpha subunits are entirely extracellular and form insulin-binding domains, while the beta subunits pass through the cellular membrane and are linked by...
proteins initiates signalling of multiple domains (4). Activation of these SH2 domain evidence exists that insulin participates in a receptors in the CNS (6, 7). In recent years, identification of both insulin and insulin-insensitive organ, in spite of the For a long time the brain was regarded as glucocorticoid levels also decrease transport of insulin into the CNS (1). Few studies have shown the synthesis of insulin in some types of neuronal tissue. Insulin mRNA has been detected in neonatal rabbit brain and neuronal cell cultures and proinsulin mRNA has been demonstrated in adult rat brain while other studies could not confirm these results (1). Moreover, immunohistochemical studies showed uniform distribution of insulin in the brain of adult mammals in opposite of concentrated staining of peptides synthesized in the CNS (1). Recently, insulin expression has been detected in postmortem human brain by ultra sensitive polymerase chain reaction (10). To summarize, experimental data show that most of the insulin in the brain is derived from pancreas but small quantities are synthesized locally in the neural tissue.

Insulin receptors are widely distributed in the CNS with highest concentrations in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus and pituitary intermediate lobe (2, 4). Areas with high levels of insulin receptors correspond to the areas with the highest insulin levels (1). In the adult mammalian brain two types of insulin receptors are found: peripheral type found only on glial cells and brain-specific type found on neurons (1). The brain insulin receptor has a lower molecular weight of both α and β subunits than the peripheral insulin receptors as a result of alternative mRNA splicing and differential glycosylation. Most of the insulin receptors are expressed on neurons and very little is observed on glial cells (1). In the brain, insulin is involved in multiple region-specific regulatory mechanisms including neuronal survival, learning and memory, regulation of energy homeostasis and reproduction (5). The present review summarizes recent data on the effect of brain insulin signalling on the control of interrelated food intake and body weight and life-span and as well on learning and memory.

Phosphorylated IRS proteins serve as multi- site docking proteins for various effector molecules possessing src homology 2 (SH2) domains (4). Activation of these SH2 domain proteins initiates signalling of multiple downstream pathways such as phosphatidylinositol 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) cascades. Thus, the insulin signal is transmitted to a branching series of intracellular pathways that regulate cell differentiation, growth, survival, and metabolism. Work with transgenic mice suggests that most insulin responses are mediated by IRS1 or IRS2 (5).

The formed insulin-insulin receptor complex is endocytosed into the cell cytoplasm, a phenomenon which accounts for the down-regulation of insulin receptor activity following insulin stimulation. After endocytosis insulin dissociates from the receptor and, following fusion of the endocytotic vesicle with cellular lysosomes, it is degraded by lysosomal enzymes. The free phosphorylated receptor may have different destiny: to be also degraded by the lysosomal enzymes, to proceed to activate other substrates or to recycle back to the surface of the cell membrane.

Insulin and insulin receptors in the brain

For a long time the brain was regarded as insulin-insensitive organ, in spite of the identification of both insulin and insulin receptors in the CNS (6, 7). In recent years, evidence exists that insulin participates in a number of normal and pathophysiological functions in the CNS. Insulin-like immunoreactivity has been shown throughout the brain (7). The origin of cerebral insulin is a matter of debate: penetration of the blood-brain barrier by pancreatic insulin or synthesis by neural tissue (1). In a number of species, such as rats, mice, dogs and rabbits, the transport of insulin from the plasma into cerebrospinal fluid has been shown after a meal or after a peripheral administration of glucose or insulin (1). It is suggested that
Role of brain insulin receptors in the control of food intake, body weight and lifespan

In the hypothalamus, insulin regulates food intake, body weight, peripheral fat deposition, hepatic gluconeogenesis, reproductive endocrine axis, and compensatory secretion of counter-regulatory hormones to hypoglycaemia (11). An important feature of the CNS is to ensure a steady supply of energy to maintain the body economy and to prepare the organism for reproduction. Different signals must be integrated in homeostatic adjustment of food intake, energy expenditure and nutrient metabolism. A growing body of evidence shows that brain insulin is a key factor in the control of feeding and adiposity in mammals and delivery of insulin to the brain has an anorexigenic effect, leading to a reduction of body weight (5). Accordingly, mice with conditional knockout of brain insulin receptors (termed NIRKO mice) are insulin resistant, glucose intolerant and overweight (12). Blockade of hypothalamic insulin receptors by antisense oligonucleotides produces hyperphagia and weight increase (13). Brain insulin interacts with a variety of neuropeptides in the control of food intake and body weight. The secreted by adipocytes peptide leptin also has anorexigenic effect. Increased insulin and leptin activity near the ventral hypothalamus have a catabolic effect, reduce food intake and body weight. The action of both peptides is mediated by central melanocortin system: insulin and leptin increase pro-opiomelanocortin gene expression. Neuropeptide Y and glucocorticoids act antagonistically to insulin and cause an increase in food intake and body weight. Insulin receptors are particularly highly expressed in the arcuate nucleus of hypothalamus, where they are co-expressed with other neuropeptides, including the anorexigenic neuropeptide proopiomelanocortin, the precursor of α-melanocyte-stimulating hormone, and the orexigenic neuropeptide Y. The stimulation of proopiomelanocortin neurons in arcuate nucleus by insulin leads to the secretion of α-melanostimulating hormone. Interestingly, insulin injected intracerebroventrically reduced food intake 24 h after injection in male but not in female rats. The reduction of food intake by centrally administered insulin was lower in overweight animals compared to lean and normal weight animals, suggesting that disruption of insulin signalling in the brain might be involved in the development of overweight (14).

Plasma insulin levels were shown to correlate with the degree of body fat and serve as adipose signal to the brain (14). In males body fat is mainly visceral while females have subcutaneous fat. Peripheral insulin levels seem to be a better predictor for visceral fat where leptin is a better indicator for subcutaneous fat (14). Increased visceral body fat, correlated with increased blood insulin levels, is an important risk factor in the development of type2 diabetes and hypertension. So, central insulin and leptin appear to be signals to the brain for food availability, food intake (energy) and body fat (i.e. metabolic reserves) (14). High-fat diet reduced the insulin transport and uptake into the brain, resulting in increased food intake and body weight (14). NIRKO mice, deficient in brain insulin receptors, in addition to obesity showed reduced fertility due to hypothalamic dysregulation of leutenising hormone, indicating the important role of the brain insulin signalling in the regulation of reproduction (12). Women, engaged in vigorous exercise, have reduced body fat store and consequently can have delayed puberty, menstrual disturbances and reproductive capacity. Usually such women have decreased circulating insulin, leptin and pituitary reproductive hormones (15). These observations suggest that regulation of reproductivity depends on signals such as insulin, informing the CNS that body has enough fat stores (15).

By 1997, molecules and signalling pathways homologous to the CNS insulin signalling system in mammals have been discovered in two very simple organisms: the nematode Caenorhabditis elegans and the fruit fly Drosophila melanogaster (15). Scarce food and caloric restriction in the nematode C. elegans result in decreased adaptive insulin signalling, leading to developmental arrest and long-lived larvae in dauer phase (10). Ablation of insulin-like neurosecretory cells in the Drosophila brain increased fasting glucose levels and increased storage of lipids and carbohydrates and as well reduced fertility and increased life-span, demonstrating the importance of insulin-like peptides in the regulation of fuel metabolism and life-span (4). Insulin signalling in the CNS of mammals, including humans, seems to have many biochemical, molecular, and physiological parallels with its role in invertebrates. For example, caloric restriction in mammals is associated with reduced
secretion of insulin and reproductive hormones and, if prolonged, with extension of life-span, suggesting that insulin levels may be a critical negative factor for control of aging in mammals as well (15). Longevity is associated with species, closer to the top of the food chain, with slow growth rates, large size, low predation and delayed reproduction. In general, shorter life-spans are character for heavily predated smaller species at the bottom of the food chain, adapted for rapid growth and maturation. Shorter-life spans have higher metabolic rates than larger species. Accordingly, the idea that insulin signalling, through insulin and insulin-like growth factors, has evolved not only to regulate life-span but represents metabolic code which couples the organism size and growth rates to the nutrient environment or food chain has been suggested (10).

Role of brain insulin receptors in learning and memory

Cognitive deficits in diabetes mellitus and Alzheimer's disease

Diabetes mellitus is a metabolic disorder associated with chronic hyperglycaemia. In type 1 diabetes, which generally develops at a young age, the principal defect is an autoimmune destruction of pancreatic β-cells, leading to insulin deficiency. In type 2 diabetes, which generally develops in adult and aged people, the principal defect is insulin resistance due to impaired insulin receptor activation. A number of recent studies are focused on the impact of diabetes on brain functions and the possible link between diabetes and dementia in normal aging and in neurodegenerative diseases as Alzheimer's disease (13, 16, 17). Alzheimer's disease is the most common neurodegenerative disorder in humans, manifested by a profound loss of memory. Neuropathologically, the disease is characterized by senile plaques that are composed mainly of aggregated fibrillar insoluble small peptide, called β-amyloid, and neurofibrillary tangles of hyperphosphorylated tau protein. Patients with type 1 diabetes are characterized by a mild to moderate slowing of mental speed and a diminished mental flexibility, without evident impairments of learning and memory (18). Patients with type 2 diabetes have moderate impairments of verbal memory and mental speed (16). Older adults with type 2 diabetes show consistent learning deficits and impairments on measures of attention, manual dexterity, reasoning, and psychomotor speed (9). In younger individuals with diabetes, however, no evidence of learning and memory impairment has been detected (4). In elderly patients with type 2 diabetes, the cognitive impairments may be more pronounced and even to interfere with day-to-day functioning (16). Longitudinal epidemiological studies suggest that patients with type 2 diabetes, manifested by hyperinsulinaemia, are at higher risk for cognitive decline and Alzheimer's disease compared with age-matched controls. In diabetic subjects over 70 years the incidence of dementia even appears to be doubled (13).

In diabetic patients, the volume of the amygdala and hippocampus, two brain structures important for memory processing, was shown to be reduced (13). Postmortem studies have revealed a higher number of defective insulin receptors in the brain of patients with Alzheimer's disease and as well a higher level of non-metabolised glucose in cerebral blood (14). Individuals suffering from Alzheimer's disease have lower insulin concentrations in the cerebrospinal fluid and higher plasma insulin concentrations, indicating for impaired insulin metabolism in the brain (4). Notably, treating of diabetes with insulin may ameliorate cognitive impairments (9). In conclusion, epidemiological studies indicate a link between hyperinsulinaemia and dementia or Alzheimer's disease and as well that learning and memory processes may be affected by changes in insulin levels in the periphery, pointing out the role of insulin on cognitive function. In addition, the hypothesis that abnormalities in energy metabolism in Alzheimer's disease might be due to reduced insulin action or insulin resistance in the brain was suggested (3).

Effects of insulin on experimental tests for learning and memory

Intraperitoneal injection of nonconvulsive insulin dose immediately after training significantly impaired retention of male Swiss mice tested 24 h after training in a one-trial step-through inhibitory avoidance task (19). The simultaneous administration of glucose antagonizes the actions of insulin on retention, suggesting that the hormone may have produced a hypoglycaemic response with subsequent memory impairment. Other studies showed that simultaneous injection of insulin and glucose even improved memory (13). The peripheral injection of small doses of insulin reversed scopolamine induced amnesia in a food-motivated task (13). Insulin administered
intracerebroventricularly immediately post training improved performance of a passive avoidance task in rats (1). Most of the results obtained in experimental animals in the state of euglicaeemia reveal memory-improving effects of central insulin administration. By contrast, NIRKO mice, lacking brain insulin receptors, show normal spatial learning (20), suggesting that brain insulin receptors do not play a primary, substantial role in memory formation (4). It should be stressed that deletion of insulin receptors occurs in early development of NIRKO mice and the lack of the insulin receptors could be compensated by other mechanisms (4).

Impairments in cognition have been demonstrated in a number of rodent models of diabetes (21). Streptozotocin is glucose analog, particularly cytotoxic to β-cells in the pancreas, often used to develop experimental models of diabetes mellitus. Chronically intracerebroventricular injections of streptozotocin reduce glucose and glycogen metabolism by 10 – 30% in the cerebral cortex and hippocampus. These effects are associated with reduced glucose utilization, decreased insulin signalling in spite of increased insulin binding and impaired learning. Rats with streptozotocin-induced diabetes and insulin deficiency preserved performance of simple behavioural tasks, such as passive avoidance test, whereas performance of more complex tasks, such as water maze is disturbed (21). Overall, animal model research indicates that insulin deficiency may result in impairment in cognitive processes while human studies suggest that insulin insensitivity may also affect cognitive processing (1).

The hippocampus is an important brain structure, participating in many types of learning and memory, in which insulin, independent of its glucoregulatory effect, was shown to promote learning and memory (11). High levels of insulin receptors are found in the molecular layer of the dentate gyrus and in the dendritic fields of CA1 pyramidal cells (stratum oriens and stratum radiatum) (1). Moreover, in the hippocampus insulin receptors are associated with immunodetectable phosphorytrosin and IRS-1, one of the second messenger systems of insulin action (1). Microinjection of 12 mU (but not 0,5 and 6 mU) into the CA1 region of rat hippocampus improved memory retrieval and consolidation (22). In another study posttraining insulin infusion into the same rat brain region enhanced memory in passive avoidance task (23). Spatial learning rapidly increases insulin receptor expression in the dentate gyrus and hippocampal CA1 region and modulates tyrosine phosphorylation of cytosolic and membrane proteins (24). Spatial learning also increases IRS-1 levels in hippocampal membranes shortly after training and reduces IRS-1 levels after extensive training with stable performance (24). Interestingly, gene expression of insulin receptors after learning showed a regional specificity with a persistent up-regulation only in the CA1 region and a profound down-regulation in the CA3 region (25).

Cognitive effects of insulin in healthy humans

Insulin-induced hypoglycaemia exerts deleterious effects on memory, but more recently investigators have examined the effects of peripherally infused insulin on cognitive performance during a state of euglycaemia (17). Higher insulin dose (15 mU.kg⁻¹.min⁻¹) injected intravenously to healthy young people showed a better memory performance (reproduction of world list) compared to males given a lower dose (1,5 mU.kg⁻¹.min⁻¹) (26). Another dose-response study showed that euglycaemic intravenous infusions of insulin enhanced recall of previously learned words but the effect of the highest and lowest insulin concentrations were associated with the smallest effect on cognitive performance (9). Immediate and delayed recall was improved in patients with mild-moderate Alzheimer's disease during euglycaemic hyperinsulinaemia (1.0 mU insulin.kg⁻¹.min⁻¹) and during hyperglycaemia compared to control group infused with saline (17). The results of intravenous administration of insulin are promising but the memory improving effects of insulin could be also attributed to the intravenous infusion of glucose required to maintain euglycaemia. Physiologically, insulin and glucose levels are linked, and therefore it is very difficult to separate their individual effects.

Intranasal administration of bioactive compounds has been demonstrated to deliver drugs to the brain effectively without inducing systemic side effects (17). Intranasal insulin can directly access the cerebrospinal fluid by diffusing through the olfactory epithelium (17). Elevated insulin levels can be detected in the cerebrospinal fluid within 10 minutes after intranasal insulin administration, but the levels of plasma insulin and glucose are not changed (9). Chronic intranasal treatment for two months improves verbal memory and
enhances mood in young health individuals (9). Recent studies have revealed beneficial effects of acute and long-term (8 weeks) intranasal administration of human insulin on declarative memory in humans (27). Intranasal insulin administration is much more convenient than intravenous administration and as well may offer a novel treatment strategy for disorders associated with central insulin abnormalities, such as diabetes and neurodegenerative diseases (28, 29).

CONCLUSIONS
In spite of the identification of both insulin and insulin receptors in the brain, until recently the function of brain insulin signalling was not clear. A growing body of data demonstrates that brain insulin participates in the control of different brain functions, as diverse as food intake and learning and memory processes. In accordance, insulin resistance in the brain has been implicated in pathological conditions as cognitive dysfunctions in old patients with type 2 diabetes and Alzheimer’s disease. Insulin also regulates the metabolism of β-amyloid and tau, the building blocks of amyloid plaques and neurofibrillary tangles, the neuropathological hallmarks of Alzheimer’s disease. Resistance in brain insulin signalling has also been suggested for other diseases such as multiple sclerosis, affective disorders and obesity. Intranasal insulin application and the lowering of peripheral insulin concentrations by insulin-sensitising agents such as thiazolidinediones offer novel means of improving cognitive performance.

REFERENCES


