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Chapter 11

Neuronal Insulin Receptor Signaling: A Potential Target for the Treatment of Cognitive and Mood Disorders

Toshihiko Yanagita, Takayuki Nemoto,
Shinya Satoh, Norie Yoshikawa, Toyoaki Maruta,
Seiji Shiraishi, Chihiro Sugita and
Manabu Murakami

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1. Introduction

Insulin is mainly known for its peripheral effects on the metabolism of glucose, fats, and proteins. Following the discovery of insulin by Banting and Best in 1921, major research works focused on the role of insulin in the peripheral tissues (liver, muscle and adipocytes) in regulating glucose homeostasis. During the last two decades, evidence has accumulated that insulin also exerts important actions within the central nervous system (CNS) and peripheral nervous system (PNS). Although neurons are not insulin-dependent, they are insulin-responsive (Benedict et al., 2004, 2011; de la Monte 2009, 2012; Laron 2009; Stockhorst et al., 2004; van der Heide et al., 2006).

Insulin acts as a neuropeptide in the brain to regulate food intake, body weight, mood, cognitive function, memory, neuronal survival and synaptic plasticity (Laron, 2009; Stockhorst et al., 2004). Conversely, dysregulated insulin receptor signaling (e.g. insulin deficiency and insulin resistance) in the brain is involved in the neurodegenerative disease, dementia and mood disorders (Craft and Watson, 2004; de la Monte. 2012; Rasgon & Kenna, 2005). Interestingly, intranasal insulin administration has an improving effect of learning and memory as well as mood stabilizing effect in the patients with Alzheimer's disease (AD) and healthy volunteers (Benedict et al., 2004, 2007; Reger et al., 2006, 2008). Based on these findings, novel hypothesis "Type 3 diabetes" has been proposed: insulin resistance in the brain causes AD (de la Monte & Wands, 2008; de la Monte 2012;

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Steen et al., 2005). Thus, insulin receptor signaling attracts attention as the molecular target for the treatment of cognitive and mood disorders.

In the present review, we would like to summarize the novel biological and pathophysiological roles of neuronal insulin in health and disease. In addition, we also introduce several of our findings that modulation of neuronal insulin receptor signaling by therapeutic drugs and bioactive agents via multiple mechanisms in cultured bovine adrenal medullary chromaffin cells (embryologically derived from neural crest) ; 1) enhancement of insulin receptor signaling by nicotine (Sugano et al., 2006); 2) reduction of insulin receptor signaling by immunosuppressants (cyclosporine and tacrolimus) (Shiraishi et al., 2001: Satoh et al., 2008), ketone body acetoacetate (Yokoo et al., 2003), heat shock protein 90 (Hsp90) inhibitors (Saitoh et al., 2002; Yoshikawa et al., 2010); 3) negative-feedback regulation of insulin receptor signaling by insulin and glycogen synthase kinase-3 (GSK-3) inhibitors (lithium and valproic acid) (Yokoo et al., 2007; Nemoto et al., 2006, 2009) ; 4) neurite-like outgrowth induced by insulin (Nemoto et al., 2011), and up-regulation of cell surface voltage-dependent Na^+ channel induced by insulin, insulin-like growth factor-1 (IGF-1) and GSK-3 inhibitors (lithium and valproic acid) (Yamamoto et al., 1996, 1997; Yanagita et al., 2009, 2011).

2. Insulin and insulin receptor signaling in the brain

It is now generally thought that little or no insulin is produced in the brain itself (Woods, 2003; Banks, 2004; Laron 2009). Insulin crosses the blood-brain barrier (BBB) and enters the brain via a receptor-mediated active transport system (Baskin et al., 1987; Baura et al., 1993).

Insulin receptor is distributed in a widespread, but selective, pattern in the brain, including the olfactory bulb, hypothalamus, hippocampus, cerebellum, amygdale and cerebral cortex (Marks et al., 1990; Unger & Betz, 1998). The expression level of the insulin receptor is developmentally regulated, being higher at early stages and lower in the adult (Chiu & Cline 2010). Brain insulin receptors are present in particularly high concentrations in neurons, and in much lower levels in glia (Schwartz et al., 1992; Unger et al., 1989). Subcellularly, the insulin receptor is a component of synapses, where it concentrates at the postsynaptic density (Abbott et al., 1999; Marks et al., 1988). Cell surface insulin receptor, a member of receptor tyrosine kinase family, consists of two extracellular α- and two transmembrane β-subunits (~135 and ~95 kDa, respectively) that are encoded by the same gene and derived from the single-chain insulin receptor precursor molecule. The brain insulin receptor differs from its peripheral counterpart by having a lower molecular weight of both α- and β-subunits (Heidenreich et al., 1983). This is presumable the result of alternative mRNA splicing and differences in receptor glycosylation (Heidenreich et al., 1983; Goldstein & Dudley, 1992; Sugimoto et al., 2000). As shown in fig. 1, insulin receptor precursor undergoes translational glycosylation, intrachain disulfide-bond formation/isomerization (rearrangement), and disulfide-linked homodimerization at

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the endoplasmic reticulum (ER). The homodimeric insulin receptor precursor is proteolytically processed at the *trans*-Golgi network into the disulfide-linked $\alpha 2\beta 2$ complex, which is transported to plasma membrane (reviewed in Wada et al., 2005). Binding of insulin to the α-subunit causes autophosphorylation of the β-subunit tyrosine residues. Tyrosine phosphorylation of β-subunits induces specific recruitment of Src homology 2 (SH2) and phosphotyrosine-binding (PTB) domain containing proteins (SH2 and PTB domains are domains that recognize phosphorylated tyrosine residues). The most prominent scaffold proteins recruited to the insulin receptor are the insulin receptor substrate (IRS)-1/-2 and SHC (White, 1997, 1998). These scaffold proteins link the activated insulin receptor to downstream signal transduction pathways. Insulin binding to the insulin receptor activates two major parallel signal transduction cascades identified as the phosphoinositide 3-kinase (PI3K)/phosphoinositide-dependent kinase 1 (PDK-1)/Akt pathway and the Ras/extracellular signal-regulated kinase (ERK) pathway (van der Heide et al., 2006: Wada et al., 2005). Akt catalyzes inhibitory Ser^{21}/Ser^{9}-phosphorylation of GSK-3α/3β (Jope & Johnson, 2004; Jope et al., 2007).

3. Physiological roles of insulin in the brain

The neuronal specific insulin receptor knockout (NIRKO) mice study revealed that insulin receptor signaling in the CNS plays an important role in regulation of energy disposal, fuel metabolism, and reproduction: the inactivation of the insulin receptor had no impact on brain development or neuronal survival. However, female NIRKO mice showed increased food intake, and both male and female mice developed diet-sensitive obesity with increases in body fat and plasma leptin levels, mild insulin resistance, elevated plasma insulin levels, and hypertriglyceridemia. NIRKO mice exhibited impaired spermatogenesis and ovarian follicle maturation because of hypothalamic dysregulation of luteinizing hormone (Brüning et al., 2000). The NIRKO mice also had an impairment of the counter-regulatory response to hypoglycaemia (Fisher et al., 2005). The NIRKO mice exhibit a complete loss of insulin-mediated activation of PI3K and inhibition of neuronal apoptosis. In intact animals, this loss results in markedly reduced phosphorylation of Akt and GSK-3β, leading to substantially increased phosphorylation of the microtubule-associated protein Tau, a hallmark of neurodegenerative diseases. Nevertheless, these animals exhibit no alteration in neuronal proliferation/survival, memory (Schubert et al., 2003). Interestingly, the early postnatal inhibition of brain insulin receptor by using small interfering RNA causes structural and functional abnormalities (e.g. cerebellar hypofoliation and hypotrophy, impaired motor function, and altered expression of neurotrophins and neurotropin receptors) that resemble effects of fetal alcohol spectrum disorder (FASD). The findings suggest that major abnormalities in brains with FASD are mediated by impairments in insulin/IGF signaling. (de la Monte et al., 2011). Although there is little evidence to date from neuronal insulin receptor knockout and knockdown studies for a key role in learning and memory, there is evidence that insulin may play important roles in learning and memory (Williamson et al 2012). The deletion of IRS-2

(but not IRS-1) causes a similar phenotype; IRS-2 knockout mice displayed hypothalamic female infertility, and increased food intake and obesity (Burks et al., 2000). These findings implicate that neuronal insulin receptor ~ IRS-2 pathway plays crucial roles in the neuroendocrine regulation of reproduction and energy homeostasis. Furthermore, the disruption of the IRS-2 gene reduced neuronal proliferation during development by 50%, which dissociated brain growth from IRS-1-dependent body growth. In the old IRS-2 knockout mice, neurofibrillary tangles containing phosphorylated tau accumulated in the hippocampus, suggesting that IRS-2 signaling is neuroprotective. Thus, dysregulation of the IRS-2 branch of the insulin/IGF-1 signaling cascade reveals a molecular link between diabetes and neurodegenerative disease (Schubert et al., 2003). Indeed, intravenous and intranasal administrations of insulin improve cognitive performance in a humans and animals in a wide variety of settings, including healthy subjects, aged subjects, AD patients and in the various experimental models of insulin resistance (Reagan 2007; Stockhorst et al., 2004: Wada et al., 2005; Watson & Craft, 2004).

4. Insulin resistance and cognitive disorders

The intensively studied phenomenon of insulin resistance in peripheral tissues is tightly linked with overweight and a hallmark in the development of type 2 diabetes mellitus (T2DM). Insulin resistance and impaired glucose tolerance are considered early warning signs for the development of T2DM. Cognitive impairments are more common in diabetic patients than in non-diabetic subjects. In the Rotterdam study, of 6,370 elderly subjects studied for 2.1 years, 126 developed dementia; 89 of these were specifically diagnosed with AD. T2DM doubled the risk of a patient having dementia and patients on insulin had four times the risk (Ott et al., 1999). Hisayama Study in Japan also revealed that impaired glucose tolerance (an early warning sign of T2DM) increased risk of all-cause dementia (Ohara et al., 2011). This T2DM-associated dementia is in part due to ischemic events resulting from cerebral microvascular and/or macrovascular disease or to repeated episodes of severe hypoglycemia. These conditions have been referred to as secondary diabetic encephalopathy. However, there is accumulating evidence suggesting that cognitive dysfunction is also caused by diabetic dysmetabolism in the brain, so-called primary diabetic encephalopathy (Ott et al., 1999; Sima et al., 2004; Sima & Li. 2006).

Cerebral insulin resistance could be the result of various mechanisms at different levels. Acute elevations of plasma insulin levels have been found to correlate with cerebro-spinal-fluid (CSF) insulin concentrations in healthy, normal weight humans. However, in overweight humans, the ratio of CSF to plasma insulin seems altered – elevated plasma insulin levels due to peripheral insulin resistance are not accompanied by similar elevations in cerebral insulin levels (Ketterer et al., 2011).

The peripheral and CNS insulin abnormalities have been reported in AD patients. AD patients have an increased risk for hyperinsulinemia and hyperglycemia relative to healthy controls (Meneilly et al., 1993; Razay and Wilcock, 1994), and also have lower CSF insulin

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levels, higher plasma insulin levels, and reduced insulin-mediated glucose disposal, a pattern consistent with insulin resistance (Craft et al., 1999; Watson & Craft 2006). AD brains show reduced insulin receptor density and tyrosine kinase activity markers (Frölich et al., 1998). The expression of insulin receptor was increased in the hippocampal dentate gyrus and CA1 field following training of rodents on a spatial memory task, suggesting that neuronal insulin sensitivity could be enhanced during learning (Zhao et al., 1999). In addition, intravenous and intranasal administrations of insulin improve cognitive performance in AD patients and in the experimental models of insulin resistance (Wada et al., 2005; Watson & Craft, 2004). Taken together, these correlative findings suggest that insulin resistance in the brain may be associated with AD.

Moreover, de la Monte et al., proposed novel disease concept "Type 3 diabetes": AD is a brain DM (Steen et al., 2005; de la Monte and Wands, 2008). Postmortem brain studies demonstrated that the molecular, biochemical, and signal transduction abnormalities in AD are virtually identical to those that occur in T1DM and T2DM (see review de la Monte & Wands, 2008; de la Monte 2012). In addition, experimental brain diabetes produced by intracerebral administration of streptozotocin shares many features with AD, including cognitive impairment and disturbances in acetylcholine homeostasis. This experimental brain diabetes is treatable with insulin sensitizer agents, i.e., drugs currently used to treat T2DM (de la Monte & Wands, 2008).

5. Insulin resistance and mood disorders

Evidence has accumulated that obesity is associated with mood disorders. Obesity is associated with an approximately 25% increase in odds of mood and anxiety disorders and an approximately 25% decrease in odds of substance use disorders (Simon et al. 2006). The individuals meeting criteria for obesity are more likely to report a major depressive episode in the past 12 months when compared to healthy weight individuals (Chen et al. 2009). Prospective studies add further evidence that obesity is a significant risk factor for depression, although depression did not increase the risk of future obesity (Roberts et al. 2003).

Numerous studies describe the association between insulin resistance and depression. Low glucose utilization rates as well as abnormal glucose and insulin disposal rates have been reported in a significant proportion of patients with depressive disorders (Ramasubbu 2002; Rasgon & Kenna 2005). The evidence lending support to this association is the influence of therapeutic drugs for depression (e.g. selective serotonin-reuptake inhibitors (SSRIs) and tricyclic antidepressants) on insulin resistance. Improvement in insulin resistance has been reported with successful treatment of depression with SSRIs, but worsening of insulin resistance has been reported with tricyclic antidepressants (Rasgon & Kenna 2005; Sockynska et al., 2011). Furthermore, hyperinsulinemia, a feature of peripheral insulin resistance, may in part be responsible for decreased appetite and weight loss observed in depressive disorders (Licinio-Paixao, 1999).

Although precise mechanisms that insulin resistance induces mood disorder are not revealed, impairment of multi-neuroregulatory functions of insulin (e.g. CNS glucose metabolism, BBB transport and neuroprotective effect) caused by insulin resistance in the brain may contribute to evolution and progression of serious mental disorders including depression (Ramasubbu 2002).

6. Intranasal administration of insulin

Intranasal delivery is a noninvasive method of bypassing the BBB to deliver therapeutic agents to the brain and spinal cord. The use of intranasal administration to target therapeutics to the CNS has many benefits (safety, cost, and easy handling) in the treatment of neurologic disorders, and has been used to target a wide variety of therapeutics to the CNS [e.g. Nerve growth factor (Chen X-Q et al., 1998), IGF-1 (Thorne RG et al., 2004), glucagon-like peptide-1 antagonist, exendin9–39 (Banks WA et al., 2004) and carbamazepine (Barakat NS et al., 2006)]. Intranasal administration of insulin provides direct access of the hormone to the CSF within 30 min without substantial uptake into the bloodstream (Born et al., 2002). Direct delivery of therapeutics from the nose to the brain was initially attributed to the olfactory pathway (Thorne et al., 1995). More recently, the contribution made by the trigeminal pathway to intranasal delivery to the CNS has also been recognized (Thorne RG et al., 2004). Because intraneuronal transport of neuropeptides from the nasal cavity to the olfactory bulb takes several hours (Thorne et al., 1995), extra-neuronal passage through intercellular clefts of the olfactory epithelium is assumed to be the preferential pathway of peptide transport into the CNS compartment (Ott et al., 2012).

Intranasal insulin improves memory function both in healthy humans and AD patients. Chronic (8 weeks) administration of intranasal insulin in cognitively normal young adults is associated with increased memory performance (Benedict et al., 2004, 2007). Intranasal insulin has also been studied in cognitively impaired patients. Intranasal insulin treatment produced significant memory improvement in memory-impaired subjects (early stage AD or amnestic mild cognitive impairment) (Reger et al., 2006, 2008). Interestingly, memory-improving effects of intranasal insulin were found only in non-carriers of the APOE4 gene allele that is linked to an increased risk of developing AD (Cummings and Cole, 2002), whereas the APOE4-postive subjects showed no benefits or even a decline in memory function (Reger et al., 2006). In addition, intranasal insulin administration to obese males over 8 weeks caused improvement of declarative memory and mood without reduction in body weight and fat (Hallschmid et al., 2008). Thus, the enhancement of insulin signaling in the CNS by intranasal insulin administration may be a useful approach in the treatment and/or prevention of cognitive and mood dysfunction.

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7. Modulation of neuronal insulin receptor signaling by therapeutic drugs and bioactive agents.

There are two major approaches to improve insulin signal impairment: 1) stimulation of insulin receptor signaling by insulin such as intranasal administration of insulin, and 2) adjustment of insulin receptor signaling via modulation of expression and function of insulin receptor signaling molecules. We have previously reported that several therapeutic drugs and bioactive agents affect cell surface density of insulin receptor and protein levels of IRS-1, IRS-2 and other various downstream signaling molecules via multiple intracellular mechanisms in cultured bovine adrenal medullary chromaffin cells. In this part, we would like to introduce several of our findings that the modulation of neuronal insulin receptor signaling by therapeutic drugs and bioactive agents (Fig. 1).

7.1. Nicotine and protein kinase C-α (PKC-α) activation: enhancement of insulin receptor signaling via increase in IRS-1, IRS-2, and cell surface insulin receptor (Fig.1 ① and ①').

Activation of neuronal nicotinic acetylcholine receptors (nAChRs) enters Na^+ into the cells and rapidly evokes excitatory postsynaptic potentials and Ca^{2+}-dependent exocytosis of neurotransmitters, while generating longer-lasting multiple effects (e.g. synaptic plasticity, learning and memory, and cell survival) (Dajas-Bailador & Wonnacott 2004; Sugano et al., 2006). The aberrant down-regulation of nAChRs accounts for cognitive deficits in normal aging and age-related neurodegenerative diseases, such as AD (Picciotto & Zoli 2002), with impairment of acetylcholine synthesis in AD brain (Hoshi et al. 1997). Enhancement of nAChRs signaling caused by choline esterase inhibitors is the major therapeutic strategy against these cognitive impairments, but the therapeutic mechanisms have not been fully identified at the cellular level (Newhouse et al. 2001; Nordberg 2001; Picciotto and Zoli 2002).

In cultured bovine adrenal chromaffin cells treated with nicotine (10 μ M for 24 h), insulin (100 nM for 10 min)-induced phosphorylation of Akt, GSK-3β and ERK1/2 was enhanced by ~62%, without altering levels of these protein kinases. Treatment with nicotine produced time (≧ 12 h)- and concentration (EC_{50} = 3.6 and 13 μ M)-dependent increases in IRS-1 and IRS-2 levels by ~125 and 105%, without altering cell surface density of insulin receptor. Nicotine also increased IRS-1 and IRS-2 mRNA levels by ~57 and ~50%. Nicotine-induced increase in IRS-1 and IRS-2 was prevented by nAChR antagonists (d-tubocurarine and mecamylamine), cell membrane-permeable Ca^{2+} chelator (BAPTA-AM), protein synthesis inhibitor (cycloheximide), transcription inhibitor (actinomycin D), conventional protein kinase C (cPKC) inhibitor (Gö6976), or ERK kinase inhibitor (PD98059 and U0126). Nicotine phosphorylated cPKC-α, thereby increasing phosphorylation of ERK1/ERK2, as demonstrated by using Gö6976, PD98059 or U0126. Selective activation of cPKC-α by thymeleatoxin mimicked these effects of nicotine. Interestingly, activation of PKC-α by thymeleatoxin or other phorbol esters up-regulated cell surface insulin receptor via transcriptional/translational events (Yamamoto et al., 2000), although nicotine did not affect cell surface insulin receptor. Thus, stimulation

of nAChRs up-regulates expression of IRS-1/IRS-2 via Ca^{2+} -dependent sequential activation of cPKC-α and ERK, and enhances insulin-induced PI3K/Akt/GSK-3β and ERK signaling pathways (Sugano et al., 2006). This nicotine-induced enhancement of insulin receptor signaling may contribute to the neuroprotective effects of nicotine.

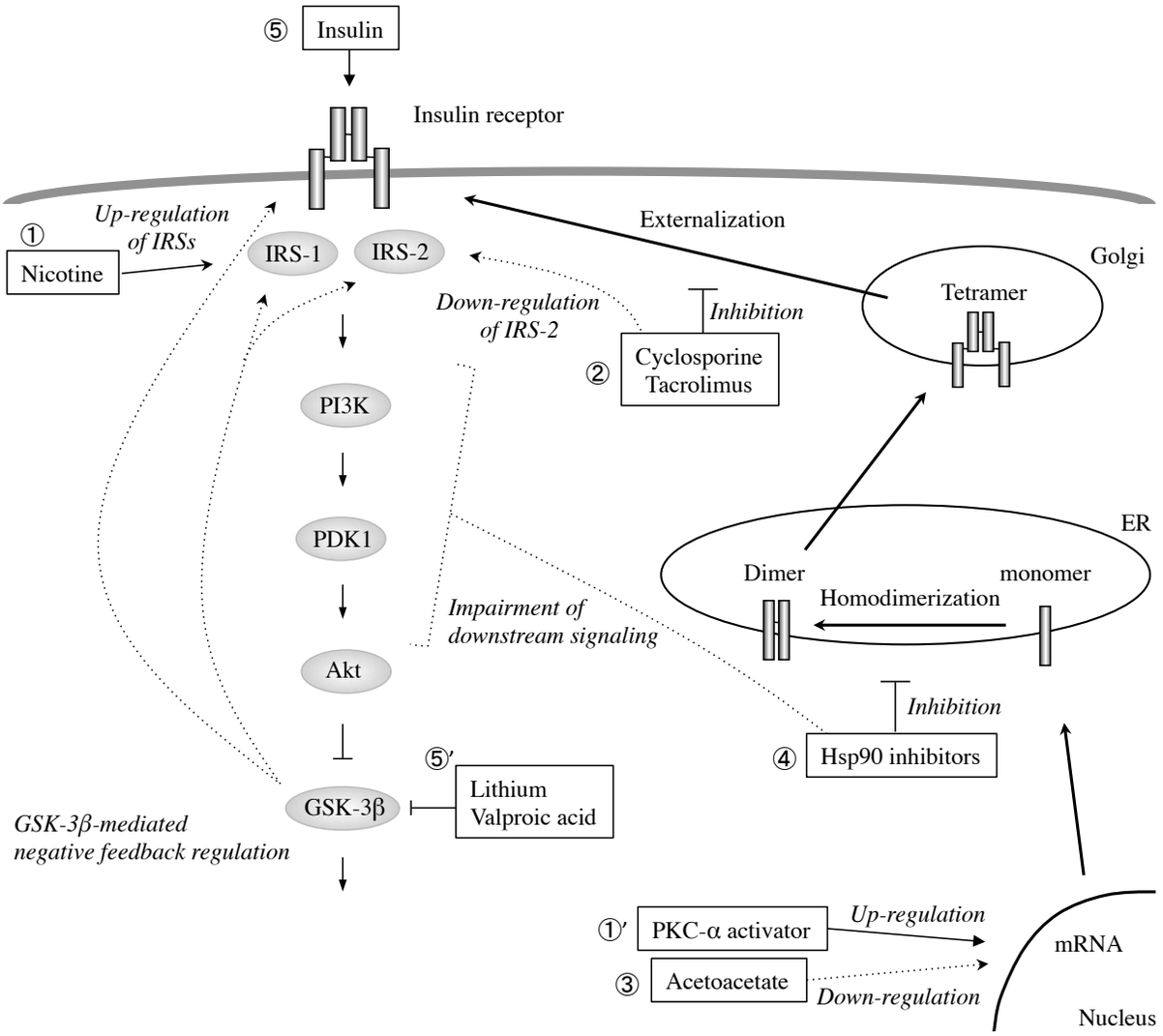

Figure 1. Modulation of insulin receptor signaling by therapeutic drugs and bioactive agents via multiple intracellular mechanisms in adrenal chromaffin cells. ① and ①′: Nicotine-induced up-regulation of IRS-1 and IRS-2, and PKC-α activation-induced up-regulation of insulin receptor (see 7-1).②: Immunosuppressants (cyclosporine and tacrolimus)-induced down-regulation of cell surface insulin receptor and IRS-2 (see 7-2).③: Acetoacetate-induced down-regulation of insulin receptor.④: Hsp90 inhibition-induced impairment of insulin receptor signaling via down-regulation of cell surface insulin receptor and various downstream signaling molecules (e.g. IRS-1, PI3K, PDK-1, Akt, GSK-3β, and Raf-1) (see 7-4). ⑤ and ⑤′: GSK-3β-mediated negative feedback regulation of insulin receptor signaling caused by chronic treatment with insulin and GSK-3 inhibitors (lithium and valproic acid) (see 7-5).

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7.2. Immunosuppressants, cyclosporine and tacrolimus: reduction of insulin receptor signaling via down-regulation of cell surface insulin receptor and IRS-2. (Fig.1②)

Cyclosporine (Cyclosporin A) and tacrolimus (FK506) are clinically important immunosuppressive drugs that are widely used to prevent organ rejection after transplantation. In addition, an increasing number of autoimmune diseases are treated with these drugs (Oetjen et al., 2003). Both structurally distinct drugs bind to their respective intracellular receptors, the immunophilins, and the drug-immunophilin complexes then bind to and inhibit calcineurin phosphatase; this inhibition of calcineurin is well known as the mechanism of immunosuppressive effect (Ho et al., 1996). In addition, cyclosporine and tacrolimus directly inhibit peptidyl prolyl *cis-trans* isomerase (PPIase) activity of immunophilin (Shiraishi et al., 2000). Among the most serious adverse effects of cyclosporine and tacrolimus are the impaired glucose tolerance leading to hyperglycemia and DM (Kahan, 1989, 1994; Jindal et al., 1997; Saltiel, 2001; Oetjen et al., 2003) as well as neurotoxicity (Bechstein 2000; Gijtenbeek et al., 1999). The incidence of glucose tolerance has been estimated to be 10 to 30% (Kahan, 1989; Jindal et al., 1997; Oetjen et al., 2003). Between 10~28 % of patients who receive cyclosporine experience some form of neurotoxic adverse event. Mild symptoms are common and include tremor, neuralgia, and peripheral neuropathy. Severe symptoms affect up to 5 % of patients and include psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motoric weakness, or leukoencephalopathy. The mechanisms of neurotoxicity associated with cyclosporine and tacrolimus are less well-understood (Bechstein 2000; Gijtenbeek et al., 1999).

Chronic (≧ 3 h) treatment of cultured bovine adrenal chromaffin cells with cyclosporin A or FK506 selectively decreased IRS-2 protein level by w50% (IC_{50} = 200 or 10 nM), without changing IRS-2 mRNA level, and protein levels of insulin receptor, IGF-1 receptor, IRS-1, PI3K / PDK-1 / Akt / GSK-3β and ERK1 / ERK2 via inhibition of calcineurin activity (IC_{50} = 500 or 40 nM, in vitro assay). Cyclosporin A and FK506 accelerated IRS-2 degradation rate ($t_{1/2}$) from >24 to ~4.2 h, without altering IRS-2 protein synthesis. IRS-2 reduction induced by cyclosporin A or FK506 was prevented by lactacystin (proteasome inhibitor), but not by calpeptin (calpain inhibitor) or leupeptin (lysosome inhibitor). Cyclosporin A or FK506 increased serine-phosphorylation and ubiquitination of IRS-2. These results suggest that calcineurin inhibition by cyclosporin A or FK506 decreased IRS-2 protein level via proteasomal IRS-2 degradation (Satoh et al., 2008). Interestingly, inhibition of PPIase activity of immunophilin by cyclosporin A or FK506 inhibits externalization of insulin receptor (but not IGF-1 receptor), and down-regulates cell surface expression of insulin receptor (Shiraishi et al., 2000). Cell surface density of IGF-1 receptor was not changed in cyclosporin A- or FK506-treated cells; however, IGF-1-induced phosphorylations of GSK-3β and ERK1/ERK2 were attenuated by ~50%. Therefore, cyclosporin A and FK506 reduced insulin receptor signaling via two mechanisms; (1) down-regulation of cell surface expression of insulin receptor via inhibition of PPIase activity of immunophilin, and (2) selective reduction of IRS-2 protein via inhibition of calcineurin. As mentioned above, knockout mice of insulin receptor, IRS-1 or IRS-2 study revealed that neuronal insulin receptor ~ IRS-2 pathway plays crucial roles

in the regulation of reproduction, energy homeostasis, cognitive performance, and neuroprotection. In addition, forebrain-specific calcineurin knockout mice exhibit impairment of bidirectional synaptic plasticity, working/episodic-like memory, and multiple abnormal behaviors related to schizophrenia (miyagawa et al., 2003; Zeng et al., 2001). Thus, this reduction of insulin receptor signaling might be involved in the neuronal disorders caused by immunosuppressants. Our findings raise a possibility that intranasal insulin administration might be effective in the treatment for immunosuppressants-induced neuronal disorders.

7.3. Ketone body acetoacetate: reduction of insulin receptor signaling via down-regulation of cell surface insulin receptor. (Fig.1③)

It has been widely accepted that glucose is the main energy source in the brain. However, in some circumstances, such as diabetes, starvation, during the suckling period and the ketogenic diet, brain uses the ketone bodies, acetoacetate and β-hydroxybutyrate, as energy sources (Massieu et al., 2003; Nehlig & Pereira de Vasconcelos, 1993). Ketone body utilization in brain depends mainly on its blood concentration, which is normally very low, but increases substantially during the conditions mentioned above (Massieu et al., 2003), although astrocyte can produce ketone body (Guzmán & Blázquez 2004). Under normal conditions, blood levels of ketone bodies are maintained below 0.5 mM (Sokoloff, 1973), but, during fasting or a high-fat, low-protein, and low-carbohydrate diet, blood levels of ketone bodies become elevated (referred to as ketosis) (Massieu et al., 2003; Noh 2006). Previous studies have demonstrated that, during starvation or administration of ketone bodies, the ketone bodies have neuroprotective effects against hypoxia / ischemia- and glutamate-induced neuronal damage toxicity, AD, and Parkinson's disease (Maalouf et al., 2009; Massieu et al., 2003; Noh 2006). Ketone bodies are converted from free fatty acid (FFA) when there is not enough insulin. The increased level of FFA is linked to the insulin-resistance in DM and obesity because FFA interferes with insulin's intracellular signaling (Boden et al., 2001; Patti, 1999). Diabetic ketoacidosis is a severe and life threatening metabolic disease caused by an absolute or relative deficiency of insulin (Wolfsdorf et al, 2009; Yokoo et al., 2003). Cerebral edema is the most important neuronal complication of diabetic ketoacidosis as it is associated with a high mortality rate of 20 to 90 %. Of the survivors, 20 to 40 % suffer from serious and permanent neurologic disability including motor deficits, visual impairment, seizure disorder, learning disability and speech disturbance. Clinically, apparent cerebral edema occurs in approximately 1% of episodes of diabetic ketoacidosis, and the pathogenesis of diabetic ketoacidosis-related cerebral edema is unclear and incompletely understood (Glaser 2009; Shastry & Bhatia 2006; Wolfsdorf et al, 2009).

Chronic (≧ 24 h) treatment of cultured bovine adrenal chromaffin cells with ketoacidosis-related concentrations (≧3 mM) of acetoacetate (but not β-hydroxybutyrate, acetone, and acidic medium) caused a time- and concentration-dependent reduction of cell surface insulin receptor by ~38%. Acetoacetate decreased protein and mRNA levels of insulin receptor via shortening insulin receptor mRNA half-life (stability). In cells treated with

acetoacetate (10 mM, 24 h), insulin-induced (100 nM for 10 min) tyrosine-phosphorylation of IRS-1 was attenuated by 56% in acetoacetate-treated cells, with no change in IRS-1 level. These results suggest that chronic treatment with ketoacidosis-related concentrations of acetoacetate (but not β-hydroxybutyrate and acetone) down-regulated the density of cell surface insulin receptor, thereby reducing insulin receptor signaling (Yokoo et al., 2003). Further in vivo and in vitro investigations are required to elucidate the relationship between the acetoacetate-induced impairment of neuronal insulin receptor signaling and the diabetic ketoacidosis-related neuronal damages.

7.4. Hsp90 inhibitors: impairment of insulin receptor signaling via down-regulation of cell surface insulin receptor and various downstream signaling molecules. (Fig.1④)

Hsp90 is the most abundant molecular chaperone in eukaryotic cells (Welch and Feramisco, 1982). It has been increasingly recognized that Hsp90 plays a important role in the regulating signal transduction pathways that control cell proliferation and cell death, since its chaperone function is restricted to a subset of proteins including nuclear hormone receptors, tyrosine kinases, serine/threonine kinases, and transcription factors (Kamal et al., 2004; Richter and Buchner, 2001; Zhang and Burrows 2004). These findings were evidenced by using selective Hsp90 inhibitors [geldanamycin (GA), 17-allylamino-17-demethoxy-geldanamycin (17-AAG), Herbimycin A (HA) or radicicol] (Saitoh et al., 2002; Whitesell et al., 1994; Yoshikawa et al., 2010). GA binds to the adenosine nucleotide binding site of N-terminal domain of Hsp90 with affinity higher than that of ATP, inhibiting the ATPase activity/chaperone function of Hsp90 (Whitesell et al., 1994; Young et al., 2001).

In adrenal chromaffin cells, inhibition of Hsp90 by GA or HA decreased cell surface ^{125}I- insulin binding in a concentration- and time-dependent manner. GA (1 μM for 24 h) lowered the B_{max} value of ^{125}I-insulin binding by 80%, without changing the K_d value. Western blot analysis showed that GA (1 μM for 24 h) lowered $\alpha 2\beta 2$ tetramer-form of insulin receptor level by 83%, while raising insulin receptor precursor level by 100%. [^{35}S]methionine/cysteine pulse-chase study of insulin receptor revealed that monomeric insulin receptor precursor (~190 kDa) developed into the homodimeric insulin receptor precursor (~380 kDa) and the mature $\alpha 2\beta 2$ insulin receptor (~410 kDa) in nontreated cells. In contrast, in GA-treated cells, the homodimerization of monomeric insulin receptor precursor was completely blocked. GA had no effect on insulin receptor mRNA levels and internalization rate of cell surface insulin receptor. Thus, inhibition of chaperone activity of Hsp90 by GA completely blocked homodimerization of monomeric insulin receptor precursor in the ER; the dimeric insulin receptor precursor and the tetrameric mature-form of insulin receptor were significantly decreased, whereas the monomeric insulin receptor precursor was accumulated in the ER. Chaperone activity of Hsp90 is indispensable to the homodimerization of monomeric insulin receptor precursor (Saitoh et al., 2002).

GA also affects the protein levels of downstream signaling molecules of insulin receptor. GA treatment significantly decreased protein levels of IRS-1, PI3K, PDK-1, Akt, GSK-3β, and Raf-1, without altering protein levels of ERK and ERK kinase. Interestingly, GA increased protein level of IRS-2. Chronic (≧12 h) treatment with 0.1–10 μM Hsp90 inhibi-

tor (GA, 17-AAG, HA, and radicicol) decreased IRS-1 level by ~66%, while increasing IRS-2 level by ~160%. These effects of GA (IC_{50} = 155 nM, EC_{50} = 177 nM) and 17-AAG (IC_{50} = 310 nM, EC_{50} = 260 nM) were time- and concentration- dependent. GA-induced decrease of IRS-1 was attenuated by proteasome inhibitors (lactacystin, β-lactone or MG132), but not by calpain inhibitor (calpastatin) or lysosome inhibitor (leupeptin). GA-induced increase of IRS-2 was prevented by cycloheximide or actinomycin D. GA lowered IRS-1 mRNA level by ~39%, while raising IRS-2 mRNA level by ~109%, without changing the stability of IRS-1 and IRS-2 mRNA. Nuclear run-on assay revealed that GA retarded IRS-1 gene transcription by 42%, while accelerating IRS-2 gene transcription by 41%. Hsp90 inhibitors oppositely altered IRS-1 and IRS-2 levels via proteasomal degradation and gene transcription (Yoshikawa et al., 2010).

Increasing evidence has accumulated over the past 2 decades that anti-Hsp90 autoantibodies in CSF may be involved in the various neuropsychological diseases. Aberrant increase in anti-Hsp90 antibodies in CSF or blood were found in the patient with Schizophrenia (Kim et al., 2001), autism (Evers et al., 2002), acute bipolar mania (Shen et al., 2006), and multiple sclerosis (Cid et al., 2007). The autoantibodies to Hsp90 in CSF from multiple sclerosis induced cell death of cultured oligodendrocyte precursor cells (Cid et al 2005). Moreover, it has been reported that schizophrenia associated with abnormalities in glucose metabolism that may lead to insulin resistance and a 3-fold higher incidence of T2DM (Zhao et al 2006). In postmortem brain tissue from schizophrenic patients, protein level of insulin receptor β-subunit and Akt activity were drastically decreased (Zhao et al 2006). These correlative findings imply that chaperone activity of Hsp90 plays crucial roles in the regulation of various neuropsychological functions in brain via maintenance the expression and function of insulin receptor and downstream signaling molecules.

A derivative of GA, 17-AAG, has similar cellular effects of GA but lower hepatotoxicity than GA. 17-AAG exerts a potent antitumor activity in preclinical models and is currently in clinical trials (Neckers 2002). Aberrant expression of IRS-1 has been associated with pathogenesis and progression of breast cancer and prostatic cancer (Morelli et al., 2003; Reiss et al., 2000; Koda 2006). In breast cancer, IRS-1 overexpression has been associated with tumor development, hormone independence, and anti-estrogen resistance (Surmacz 2000). In hormone dependent breast cancer cell lines, the expression of IRS-1 has been correlated with estrogen receptorα (ERα, and numerous studies have demonstrated that IRS-1 is one of the central elements of ERα-IGF-1 crosstalk (Surmacz 2000). In patients with primary breast cancer, IRS-1 expression is correlated with poorly differentiation and with lymph node metastasis (Koda et al 2006). Human prostatic cancer LNCaP cells are characterized by having a frame-shift mutation of the tumor suppressor gene piedmont triad entrepreneurial network, low levels of IGF-I receptor and no IRS-1. Reiss et al. reported that ectopic expression of IRS-1 in LNCaP cells increases cell adhesion and decreases cell motility; over-expression of IGF-1 receptor, in the absence of IRS-1, causes growth arrest and a combination of IGF-1 receptor

and IRS-1 restores the transformed phenotype of LNCaP cells. These correlative findings indicated that IRS-1 expression is involved in the growth regulation of breast and prostatic cancer. Thus, the decreasing effect of 17-AAG on the IRS-1 could be contributed to the anti-tumor effect against these cancers, although our results were obtained from primary cultured bovine chromaffin cells. In addition, previous studies with IRS-1 knockout mice or the cells derived from these mice have suggested that IRS-2 could compensate for IRS-1 deficiency more effectively in liver and pancreatic cells than in skeletal muscle, fibroblasts, or adipocytes (Tanemoto et al. 1994; Bruning et al 1997; Sesti et al. 2001). It has been shown that IRS-2 has a major role in regulating hepatic glucose production and in controlling pancreatic cell development and survival (Sesti et al. 2001). Indeed, IRS-2 knockout mice exhibit insulin resistance with abnormal glucose tolerance at birth and progressively develop fasting hyperglycemia as a result of inadequate compensatory insulin secretion because of pancreatic β-cell apoptosis (Kubota et al. 2000; Withers et al. 1998). Thus, the increasing effect of 17-AAG on the IRS-2 expression would be convenient for avoiding side effects such as hyperglycemia, insulin resistance, and pancreatic β-cell damage, during anti-cancer therapy by 17-AAG. Therefore, it is interesting to investigate precisely the down- and up-regulation of IRS-1 / IRS-2 by 17-AAG in the animal model, *in vivo* study.

7.5. Insulin, IGF-1 and potent GSK-3 inhibitors (lithium and valproic acid): negative feedback regulation of insulin receptor signaling. (Fig.1 ⑤ and ⑤′)

Control over insulin signaling can be achieved by autoregulation, whereby insulin-stimulated downstream components (e.g. Akt, GSK-3β, mTOR, and ERK1/2) inhibit upstream elements (negative feedback control; autologous regulation). The insulin receptor and the IRS proteins are targets for these feedback control mechanisms, with phosphorylation of IRS proteins on Ser / Thr residues being a key step in these feedback control processes. For example, Ser / Thr-phosphorylation of IRS-1 caused by downstream signals of the PI3K pathway (e.g., mTOR) results in the self-attenuation of IRS-1 activity. Additionally, signals from apparently unrelated (heterologous) pathways also inhibit insulin signaling. The agents inducing insulin resistance (e.g., tumor necrosis factor-α) increase Ser / Thr-phosphorylation of IRS-1 via activating protein kinases (e.g., c-Jun N-terminal kinase) and caused negative feedback regulation of insulin receptor signaling (Boura-Halfon & Zick 2009; Copps & White.2012; Zick 2001).

GSK-3, a serine/threonine protein kinase, is constitutively active in nonstimulated cells, causing phosphorylation and inactivation/degradation of various signaling molecules (e.g., glycogen synthase), transcription factors (e.g., β-catenin), translation initiation factor eIF2B, and structural proteins (e.g., tau) (Jope & Johnson, 2004; Jope et al., 2007; Meijer et al., 2004; Nemoto et al., 2006). Insulin- or IGF-I-induced activation of Akt increases Ser^{21}/Ser^{9} phosphorylation of GSK-3α/-3β and inhibits catalytic activity of GSK-3α/-3β.

In adrenal chromaffin cells, insulin activated insulin receptor but not IGF-1 receptor, whereas IGF-1 activated both insulin receptor and IGF-1 receptor (Yanagita et al., 2011). Insulin treatment increased Ser^9-phosphorylated GSK-3β level by 47% within 1 min, with peaking to 104% increase at 1 h and declining to 57% increase at 24 h (Nemoto et al., 2006). IGF-1 (100 nM) also increased Ser^9-phosphorylated GSK-3β level within 1 min, and inhibited GSK-3β activity. The maximum inhibition of GSK-3β activity (~50%) was observed at 1 min after treatment with 100 nM IGF-1, and inhibition of GSK-3β activity was continued for up to 24 h (Yanagita et al., 2011). Inhibition of GSK-3β by chronic treatment with insulin, IGF-1, lithium or valproic acid up-regulated cell surface $Na_V1.7$ Na^+ channel via acceleration of Na^+ channel α-subunit gene transcription, thereby resulting in the enhancement of Na^+ influx, Ca^{2+} channel gating and catecholamine secretion (Yamamoto et al., 1996, 1997; Yanagita et al., 2009, 2011). Chronic insulin treatment also up-regulated tau protein via acceleration of protein synthesis, and induced neurite-like process outgrowth (Nemoto et al., 2011).

In addition to these physiological effects of insulin, chronic insulin treatment down-regulated cell surface density of insulin receptor via reduction of insulin receptor mRNA stability (Yokoo et al., 2007), and protein levels of IRS-1 and IRS-2 via regulating proteasomal degradation and/or synthesis of IRS-1 and IRS-2 (Nemoto et al., 2006). These insulin-induced negative feedback regulations of insulin receptor and IRS-1/-2 were mimicked by treatment with potent GSK-3 inhibitors (lithium, valproic acid, or SB216763) (Nemoto et al., 2006, 2009; Yokoo et al., 2007). LiCl (20 mM) decreased cell surface ^{125}I-insulin binding and insulin receptor protein levels by ~48% in a time-dependent manner. LiCl destabilized insulin receptor mRNA ($t_{1/2}$ = 9.3 vs. 6.5 h), decreasing insulin receptor mRNA level by ~47%, without altering insulin receptor gene transcription (Yokoo et al., 2007). LiCl also decreased protein levels of IRS-1 and IRS-2 by ~38 and ~48% in a concentration- and time-dependent manner. Proteasome inhibitors (β-lactone or lactacystin) completely blocked LiCl-induced reduction of IRS-1, and partially blocked LiCl-induced reduction of IRS-2. LiCl lowered IRS-2 mRNA level, with no effect on IRS-1 mRNA level (Nemoto et al., 2006). These findings suggest that long-term treatment with insulin, lithium or valproic acid causes negative feedback regulation of insulin receptor signaling via inhibition of GSK-3, thereby withdrawal of these therapeutic drugs after long-term treatment may occurs severe depletion of insulin signaling.

8. Conclusion and future perspectives

Multiple lines of experiments in the last two decades have accumulated compelling evidence that brain insulin receptor signaling plays pivotal roles in regulating brain region-specific pleiotropic function, including cognitive and mood stabilizing function. Aberrant decrease in brain insulin receptor signaling (e.g. insulin resistance) may be

involved in the various cognitive and mood disorder. There are two major approaches to improve insulin signal impairment: 1) stimulation of insulin receptor signaling by insulin such as intranasal administration of insulin and 2) adjustment of insulin receptor signaling via modulation of expression and function of insulin receptor signaling molecules. The information of up- and down-regulation of insulin receptor signaling by various therapeutic drugs may provide a new avenue for the prevention and treatment of neurodegenerative disease, dementia and mood disorders.

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Author details

Toshihiko Yanagita[1], Takayuki Nemoto[1], Shinya Satoh[2], Norie Yoshikawa[3], Toyoaki Maruta[4], Seiji Shiraishi[5], Chihiro Sugita[1] and Manabu Murakami[1]

1 Department of Pharmacology, Miyazaki Medical College, University of Miyazaki, Japan

2 Department of Otorhinolaryngology, Miyazaki Medical College, University of Miyazaki, Japan

3 Department of Orthopaedic Surgery, Miyazaki Medical College, University of Miyazaki, Japan

4 Department of Anesthesiology, Miyazaki Medical College, University of Miyazaki, Japan

5 Cancer Pathophysiology Division, National Cancer Center Research Institute, Tokyo, Japan

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