The Role of SOCS-3 in Leptin Resistance and Obesity

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ABSTRACT

Obesity is one of risk factors of various chronic diseases and malignancy. It may result from excess accumulation of body fat. This condition may be caused by dysfunction of appetite-regulating pathways and energy balance due to leptin resistance. Leptin, a 16 kDa hormone, is the most important regulator of appetite and energy balance in the body. Most individuals with obesity have leptin resistance characterized by increased leptin blood level.

Some possibilities of mechanism involved in leptin resistance have been proposed by researchers despite the fact that it is still being studied hitherto. One of the mechanisms considered to have a role in leptin resistance is disruption in signal transduction process through Janus-activating kinase2-signal transducer and activator of transcription 3 (JAK2-STAT3) pathway on leptin receptors by suppressor of cytokine signaling-3 (SOCS-3).

SOCS-3 is a protein that inhibits the signal transduction process of various cytokines in the body, including leptin. SOCS-3 expression is induced by leptin and SOCS-3 activation will inhibit STAT3 phosphorylation which is important in signal transmission on leptin receptors. Such inhibition will consequently cause leptin resistance characterized by dysfunction of leptin biological function.

Key words: *SOCS-3, leptin resistance, obesity.*

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INTRODUCTION

Obesity has been developed into a global epidemic and it has been predicted that obesity of the world's population will continuously increase to date, it is estimated that more than one billion of world's population is overweight, and at least 300 million of them can be categorized as obese.[1] In some countries, such as China and Japan, the prevalence of population with obesity is 5%. In the United States, almost 57% of their population is obese. An Indonesian survey in 1997 demonstrated that the prevalence of population with overweight condition was 8.1% in adult male and 10.5% in adult female; while obesity occured in 6.8% in adult male and 13.5% in adult female.[2]

Obesity and overweight are risk factors in chronic disease, including diabetes mellitus type 2, cardiovascular diseases[1,3-5] and some malignancy conditions[5] such as colorectal cancer[2] and breast cancer.[6] In developing countries, obesity may have effect on the national health cost, i.e. it will spend 7% of total national health budget.[1]

DEFINITION AND MEASUREMENT OF OBESITY

Obesity is a state of excess adipose tissue mass.[7] The diagnosis of obesity either for medical concern or data collection of obesity prevalence is based on body mass index (BMI), which is equal to weight/height^2 in kg/m^2.[3]

MECHANISM OF OBESITY

Obesity is a kind of appetite regulation and energy balance disorder.[8] Excessive eating disorder found in obese individual is an integrated result of appetite regulation controlled by nervous system, metabolic factors and hormonal function.[7]

Some signals in the body are assumed to have roles in this regulating mechanism, including hypothalamic neuropeptides and neurotransmitters, peripheral insulin level and leptin brain level, as well as input through afferent and efferent nerve fibers. Physiologically, human body tends to maintain energy balance.[9] Human body weight is a reflection of balance between energy

Table 1. Classification of overweight and obesity based on BMI and abdominal circumference based on the Asia Pacific criteria

Classification	BMI (kg/m^2)	Co-morbidity risk	
		Abdominal circumference	
		< 90 cm (male) <80 cm (female)	≥ 90 cm (male) ≥ 80 cm (female)
Underweight	< 18.5	Low (increased risk on other clinical problems)	Moderate
Normal Range	18.5 – 22.9	Moderate	Increase
Overweight	≥ 23.0		
• At risk	23.0 – 24.9	Increase	Moderate
• Obese I	25.0 – 29.9	Moderate	Severe
• Obese II	≥ 30.0	Severe	Extremely severe

Source: WHO WPR/IASO/IOTF in The Asia -Pacific Perspective: Redefining Obesity and it's Treatment (2000)

intake and energy expenditure. In obesity, excessive body weight results from a shift of long-term positive energy balance, i.e. greater energy intake compared to energy expenditure.[2]

APPETITE-REGULATING PATHWAYS

Appetite regulation is an integrated function of hormonal and nervous system. Arcuate nucleus at the hypothalamus has two neuronal circuits, which are antagonize to each other. Both circuits, the appetite-stimulating and inhibiting circuits, are associated with paraventricular nucleus (PVN) and other nucleus in hypothalamus will regulate the appetite.[10] Stimulating-appetite circuit is affected by two types of neurotransmitters, i.e. neuropeptide Y (NPY) and *agouti-related peptide* (AgRP). NPY will give a signal on PVN to stimulate eating behavior[11], while AgRP acts indirectly by inhibiting the type-r melanocortin receptor, a receptor at the PVN which inhibits appetite. Inhibiting-appetite circuit includes cocaine and amphetamine regulated transcript (CART) and a large amount of pro-opiomelanocortin (POMC) that produces α-*melanocyte-stimulating hormone* (α-MSH).[10]

LEPTIN

Leptin, a product of obese gene, is a hormone secreted mainly by adipocytes and it is the most important regulator in regulating energy balance.[12] Leptin conveys triglycerides stored in the body to central nervous system.[13,14] Through its receptors at hypothalamus, leptin will activate Janus-activating kinase2 (JAK2) and signal transducer and activators of transcription 3 (STAT3), which subsequently will stimulate the release of anorexigenic peptides such as α-MSH and CART, and will inhibit orexigenic activity such as NPY and AgRP.[15] Such mechanism will regulate food intake and energy balance in accordance with information about total body fat conveyed by the leptin to central nervous system.[16]

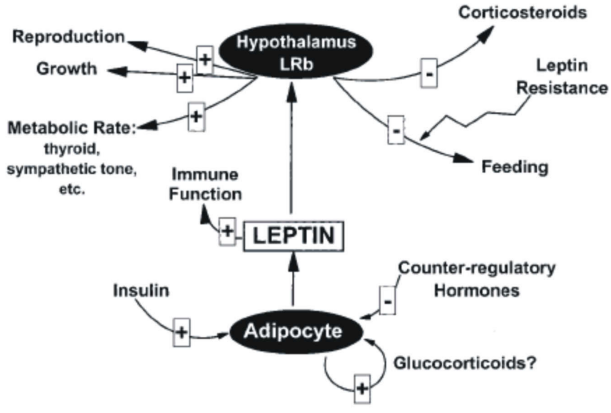

Figure 1. The biological effect of leptin

In human body, leptin has a role in regulating food intake and energy balance and as a neuroendocrine and metabolic hormone.[17] Leptin also interacts with hypothalamic-pituitary-adrenal pathway, affects the act of thyroid and growth hormones, as well as hematopoiesis, bone formation and immune system.[18]

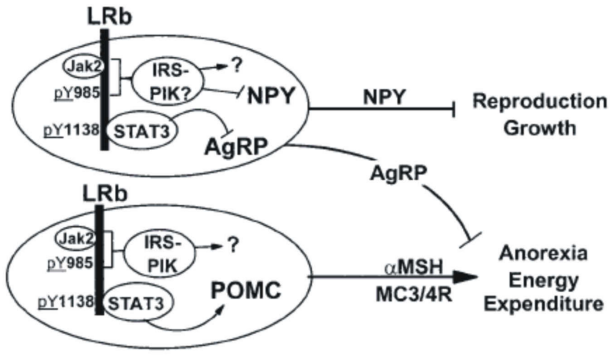

Figure 2. Mechanism of action of leptin on long-form leptin receptor (LRb)

Activation of Tyr_{1138} → STAT3 pathway on **long-form** leptin receptor (LRb) in arcuate nucleus will induce POMC, which subsequently will be processed into α-MSH that inhibits the appetite and increases body expenditure through melanocortin receptor especially melanocortin 3 receptor (MC3R) and melanocortin 4 receptor (MC4R). The role of insulin receptor substrate and phosphatidylinositol 3-kinase (IRS-PI3-K) has not been explained yet. Activation of STAT3 will also suppress AgRP expression, while other signal transduction pathway which is considered involving the IRS-PI3-K, will suppress the NPY activity and subsequently blocks the NPY inhibition against reproduction and growth axis.[19]

LEPTIN RESISTANCE

Increased synthesis of leptin mRNA and serum leptin level in obese individuals which is compared to non-obese individuals brings into a hypothesis of leptin resistance.[20] There are several causes for leptin resistance, i.e:[17]

- Receptors defect. It causes binding and activating failure of the leptin receptor. In animals, such non-functional receptors will give phenotype manifestation of early onset obesity, hyperphagia, undeveloped puberty signs and secretion disorder of GH and thyrotrophin. In humans, such receptor defect is rarely occurs.[21] Thus far, there is only a single mutation of receptor coding gene which has been reported. Such mutation causes leptin receptors to loose their intracellular and transmembrane domain.[22]
- Receptors polymorphism. It will change binding activity and signal transmission on leptin receptor.[21] This will alter the binding process either between leptin and receptor or signal transmission on leptin receptor.
- Imbalance between leptin and its binding protein in the blood. If the leptin serum level bound to carrier protein is too high, the leptin biological activity will decrease. This concept is supported by various study results revealing different ratio of free leptin level against serum leptin level bound to carrier protein in obese and non-obese individuals.[23]
- Disruption of leptin transport to the central nervous system through blood brain barrier. It is assumed that the mechanism of leptin transmission to central nervous system is mediated by the **short-form** leptin receptor (Ob-Ra) which is abundantly found in choroideus plexus. A human study indicates that ratio of leptin level in cerebrospinal fluid to serum leptin level decreases in obese individuals and the proportion of free leptin has a positive correlation to BMI.[24]
- Post-receptor defect. It causes a failure in activating neuroendocrine mediators. So far, post-receptor defect and the affected pathway have not been fully understood, but studies on it are still being developed.[17]

SUPRESSOR OF CYTOKINE SIGNALLING (SOCS)

Supressor of Cytokine Signalling (SOCS) is a protein inhibiting cytokines signal transduction.[25] SOCS protein family has eight members that have been successfully identified, i.e. SOCS-1 up to 7 and cytokine-inducible sequence (CIS).[19] The structure of SOCS protein consists of N-terminal group with varied composition and varied length of amino acid chain, a domain of src homology 2 (SH2), and a motive of C-terminal known as SOCS box.[26] SOCS protein has a role in negative feedback reaction which regulates cytokines signal transduction. SOCS protein transcription is induced by a response against cytokines expression and once it is produced, the SOCS protein will inhibit the signal transduction and various mechanisms.[27]

SUPRESSOR OF CYTOKINE SIGNALLING-3 (SOCS-3)

SOCS-3 expression is regulated by a number of cytokines in specific tissues, and thus far SOCS-3 has been proven as inhibitor of signal transduction for LIF, IL-11, GH, insulin, and leptin.[28] Infection may induce SOCS-3 expression. A study using amnion cells indicates that herpes simplex virus type 1 (HSV-1) infection increases SOCS-3 expression. Furthermore, administration of JAK3 inhibitor agents may suppress SOCS-3 expression and eventually it will inhibit viral replication of HSV-1.[29]

SOCS-3 is known to be main regulator of adrenocorticotropic hormone (ACTH) secretion and expression of POMC genes mediated by leukemia inhibiting factor (LIF). SOCS-3 may also inhibit signal transduction on LIF-activated JAK and STAT activation through a feedback negative mechanism.[30]

On the subject of diabetes mellitus and insulin resistance, SOCS-3 has been proven to inhibit proliferation of pancreatic β–cells which is induced by GH, by inhibiting signal transduction on GH receptors found in pancreatic β-cells.[31] A similar study also indicates that excessive SOCS-3 expression may disrupt glucose tolerance in oral glucose tolerance test in experimental animals.[32]

Krebs and Hilton also reported their study result that indicates SOCS-3 as an inhibitor of signal transduction pathway mediated by insulin receptors and IGF-1. SOCS-3 is bound to Tyr_{960} residue on insulin receptor and inhibits the activation of STAT5B by insulin. SOCS-3 also inhibits tyrosine phosphorylation on IRS-1 induced by insulin.[33]

SOCS-3 AND LEPTIN RESISTANCE

A study by Bjorbaek et al indicates that leptin administration on cell culture expressing long-form of leptin receptor (Ob-Rb) will induce leptin resistance.[28] The mechanism of leptin resistance is caused by induction of SOCS-3 expression by leptin. Therefore, SOCS-3 is considered to have a role in the development of such resistance. SOCS-3 induces leptin resistance through inhibition on signal transduction stage of leptin receptor without affecting receptor activity on cell surface. SOCS-3 will inhibit JAK2 phosphorylation induced by leptin.[34] Further study indicates that JAK2 and SOCS-3 will experience leptin-dependent immunoprecipitation.[28] Such result supports further on the role of SOCS-3 in developing leptin resistance.

Signal transduction pathway through Tyr_{1138} → STAT3 residue induces SOCS-3 expression. This may occur due to prolonged Ob-Rb activation that will mediate the negative feedback pathway of such signal transduction. Activated SOCS-3 will bound to phosphorylated Tyr_{985} residue and the binding will inhibit signal transduction pathway through STAT3. Other study by Myers shows that inhibition of signal transmission through STAT3 will also block JAK2 activation.

Leptin binding with the domain of extra-cellular long-form leptin receptor (LRb) will activate JAK2 *tyrosine kinase* correlated to LRb through motive Box 1 and amino acid at 31-36 chain on LRb. JAK2 activation will cause self-phosphorylation and produce Tyr_{985} and

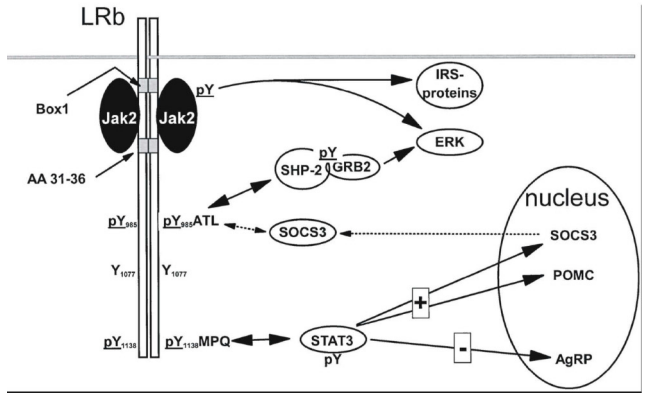

Figure 3. The role of SOCS-3 in leptin resistance

Tyr_{1138} residue at the tail of intra cellular LRb. The phosphorylated Tyr_{1138} will bind to signal transducer and activator of transcription 3 (STAT3) and mediates their own phosphorylation process. Activation of STAT3 will modulate transcription of supressor of cytokine signaling-3 (SOCS-3) and pro-opiomelanocortin (POMC) as well as inhibit transcription of agouti-related peptide (AgRP). The phosphorylated Tyr_{985} will recruit src homology 2-containing tyrosine phosphatase (SHP-2). SHP-2 will bind to and subsequently cause phosphorylation of the growth factor receptor binding 2 (Grb2) to activate signal transduction pathway that finally end as activation of extracellular signal-regulated kinase (ERK). In a prolonged stimulation, phosphorylated Tyr_{985} will also bind SOCS-3.

SOCS-3 expression is not only induced by leptin, but also by GH, LIF, ciliary neurotrophic factor (CNTF), IL-6, and other cytokines in the body tissues. A study by Bjorbaek et al indicated that serum containing various cytokines may activates SOCS-3,[16] which consequently cause a consideration that leptin resistance may also be affected by various other cytokine levels.

DISCUSSION

Prevalence and complication of obesity which will accompany the life of obese individuals creates a new paradigm of essential principles of adequate treatment for obesity and it also creates a more comprehensive understanding on physiological process providing a basis of energy balance and appetite regulation which both are disrupted in obesity. Leptin is a main hormone that conveys signal containing information of energy storage in the body and it functions to suppress energy intake as a response of adequate energy requirement.[35]

Leptin as a main regulator hormone in mechanism of appetite regulation is supported further by an evidence that neuron regulating the secretion of cholecystokinine

at the superior parabrachial nucleus and neuron regulating glucagon-like peptide-1 (GLP-1) activity at nucleus of solitarius tract are also activated by leptin.[36] Cholecystokinine is a hormone that acts in intestines to suppress appetite by retarding the gastric emptying; while GLP-1 is a hormone that is mainly produced by ileum as a response to increased nutrient, carbohydrate, and lipid level.[3] Leptin also affects secretion of adinopectin, a hormone that is considered to have a role in metabolism process, including homeostasis of glucose and catabolism of fatty acid.[37]

Leptin regulates the appetite and body weight through its interaction to neuronal circuit at hypothalamus expressing leptin receptor.[38] Leptin binding to long-form leptin receptor (LRb) will cause specific neuropeptides release and altered gene transcription that codes synthesis of certain neuropeptides. Such physiological effect can be mediated by several mechanisms, including signal transduction through JAK-STAT pathway. A recent study has demonstrated that JAK2 and STAT3 have a role in the mechanism of action of leptin on its receptors at hypothalamus.

In obesity, there is a disruption of leptin biological function, therefore leptin may loose its ability to inhibit energy intake and increase the energy expenditure which will exacerbate obesity.[39]

It has been understood that leptin treatment in individuals with obesity is limited to individuals who have congenital leptin deficiency.[40] When such treatment is given to obese individuals without leptin deficiency, the treatment does not decrease body weight.[41]

Hyperleptinemia in obesity and leptin dysfunction in executing its biological effect of suppressing appetite has brought us to an understanding that leptin resistance has been developed.[42] Such resistance may result from various mechanisms in kinetic and dynamic process of leptin, starting from leptin transportation to central nervous system up to post-receptor defect.

Some mechanisms involved in leptin resistance have been tried to be evident formerly. The first-proposed mechanism is disruption of leptin transportation penetrating the blood brain barrier.[43] Therefore, it was concluded that obesity is a blood brain barrier disease.[18]

Now, family of protein that inhibits cytokine signal transduction has been found. It has eight members, i.e. cytokine-inducible sequence (CIS) and suppressor of cytokine signaling (SOCS) 1 up to 7. The expression of SOCS protein is induced by various cytokines, including leptin and after being activated, the SOCS protein will inhibits JAK-STAT pathway.[27] A study demonstrates that leptin administration in *ob/ob* mice increases mRNA expression of SOCS-3 in hypothalamus. Increased SOCS-3 level occurs in area that largely express long-form leptin receptors (LRb). Furthermore, SOCS-3 inhibits leptin biological effect. Increased SOCS-3 expression at the arcuate and dorsomedial nuclei is found in agouti mice, i.e. hyperleptinemia mice with obese phenotype. It indicates a role of SOCS-3 as an inhibitor of leptin signal transduction and explains the role further in pathogenesis of leptin resistance.[16]

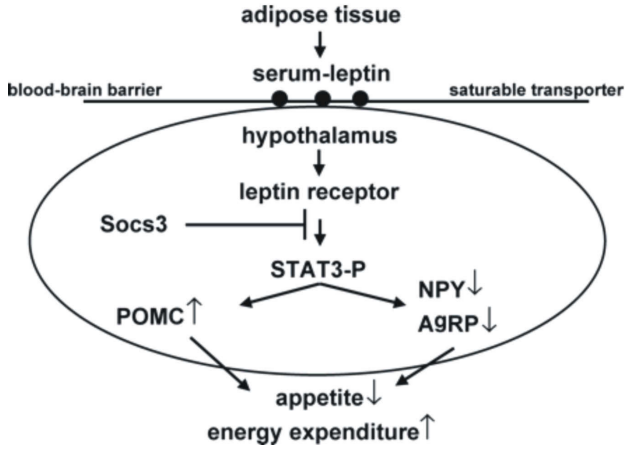

Figure 4. Mechanism of SOCS-3 in suppressing physiological effect of leptin

In hypothalamic leptin receptors, STAT3 activation by leptin will increase POMC expression as well as inhibit NPY and AgRP activity, which finally will cause inhibition of appetite and increased energy expenditure. SOCS-3 has a role in mechanism of leptin resistance through phosphorylation of STAT3.[44]

CONCLUSION

Increased prevalence of obesity in the world nowadays is an actual health issue. Unfortunately, the available drugs of agents for obesity treatment are not fully satisfying. An advance of science in revealing mystery on mechanism of leptin resistance is very useful to provide a new molecule target for anti-obesity agents.

Leptin, a peptide hormone secreted mainly by white adipocytes, will physiologically suppress the appetite. Leptin deficiency or resistance will cause excessive energy intake which will subsequently disrupt energy balance leading to obesity. Leptin resistance is found in most of individuals with obesity, while leptin deficiency is only found in small number of individuals.

SOCS-3 is a protein that inhibits the biological effect of various cytokines and it is assumed as an etiology

of leptin resistance. Increased leptin sensitivity through signal transduction pathway involving SOCS-3 is expected to be able to return the leptin biological function in regulating energy balance and disrupted food intake in individuals with obesity.

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