Estrogen and Body Weight Regulation in Women: The Role of Estrogen Receptor Alpha (ER-α) on Adipocyte Lipolysis

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ABSTRAK

Hormon estrogen memiliki peran penting dalam pengaturan metabolisme lemak. Studi terbaru menunjukan bahwa pemberian estrogen dapat menghambat lipolisis. Meskipun demikian, informasi mengenai proses molekuler yang terlibat pada fenomena ini masih sangat terbatas. Review ini bertujuan untuk menyajikan informasi mengenai berbagai macam penelitian yang menghubungkan efek dari estrogen terhadap lipolisis jaringan adiposa dan jalur molekuler yang terlibat dalam proses ini. Diperkirakan bahwa efek dari kerja estrogen terhadap penghambatan lipolisis terjadi akibat aktivasi estrogen receptor alpha (ER-α) di jaringan adiposa. Hal ini didukung oleh hasil penelitian yang menunjukan bahwa hewan coba yang tidak dapat mengekspresikan gen ESR1 memiliki penumpukan lemak yang berlebihan. Sebagai tambahan, berdasarkan studi yang dilakukan pada manusia diketahui bahwa ekspresi ESR1 di jaringan adiposa berhubungan terbalik dengan indeks massa tubuh. Penelitian lebih lanjut diharapkan dapat menguji peran ER-α terhadap lipolysis di jaringan adiposa terutama untuk melihat variasi respon ER-α terhadap program penurunan berat badan. Selain itu, ER-α juga dapat digunakan sebagai target pengembangan terapi farmakologis dan nutrisional untuk penurunan berat badan di masa depan.

Kata kunci: *jaringan adiposa, estrogen, reseptor estrogen, lipolisis, obesitas, wanita.*

ABSTRACT

Estrogen has an important role in regulation of fat metabolism. Recent studies indicated that this process occurred due to inhibition of lipolysis by external estrogen administration. However, there was limited information regarding molecular process responsible for this phenomenon. This paper was aimed to present a brief update on recent studies explaining the effect of estrogen on adipose tissue lipolysis and the molecular pathway involved in this process. It is suggested that the effect of estrogen to reduction of lipolysis was through activation of estrogen receptor alpha (ER-α) in adipose tissue. This finding is supported by the fact that mice lacking of ESR1 gene (encodes ER-α) accumulate more fat and ESR1 mRNA in human adipose tissue was inversely correlated with body mass index (BMI). Future study should be aimed to clarify the role of ER-α on lipolysis in adipose tissue during weight loss intervention. Additionally, new pharmacological or nutritional treatment with ability to modulate ER-α activity/expression could be used as a potential weight loss intervention.

Key words: *adipose tissue, estrogen, estrogen receptor, lipolysis, obesity, woman.*

INTRODUCTION

Obesity is an increasing pandemic that affects humans worldwide and World Health Organization (WHO) reported that more than 500 million people over 20 years old were obese in 2008.[1] The expert panel of WHO recommends 10% weight loss for obese and overweight individuals especially by lifestyle intervention.[2] A lifestyle intervention including diet, physical activity and behaviour modification was able to help reducing weight loss for some obese individuals, could not be applied to everyone.[3] Furthermore, with the fact that prevalence of obesity in 2008 doubled compared to 1980[1] leading to assumption that what we have done so far to prevent and treat obesity was not successful. It is suggested that some intrinsic factors affect the ability obese/overweight individuals to lose weight during a lifestyle intervention.

A growing evidence shown that lipolysis was one of the most important factor that induces weight loss.[4] Lipolysis is initiated in adipocytes to release fatty acids (FA) thus can be used as the source of energy in negative energy balance.[5] This process is controlled by sympathetic nervous system (SNS) via its receptor, beta adrenergic receptor (β-AR), and dysfunction of this receptor is related to obesity. The role of SNS in regulating lipolysis was revealed by an observation that denervation of white adipose tissue induced hypertrophy[6] and electrical stimulation of its nerve led to release of fatty acids.[7] As the mediator of SNS signals, β-AR regulates lipolysis through sequential stimulation of adenylyl cyclase and protein kinase A (PKA)[8] via a Gs protein. The catalytic subunit of activated PKA accesses hormone sensitive lipase (HSL) and perilipin then induces release of fatty acid and glycerol into circulation.[9]

In obese individuals, the sensitivity of lipolysis response by β-AR was reduced. A study by Schiffelers et al. revealed that during β2-AR stimulation, obese subjects had lesser increment in energy expenditure, plasma Non-esterified fatty acid (NEFA) and glycerol level compared to lean individuals.[10] This is supported by other evidence showing that lipolytic noradrenaline sensitivity was reduced in obese women compared to non-obese women.[11] It was also observed that obese women had reduction in surface density of β2-AR.[11]

Investigating β-AR induced lipolysis in obese individuals is important because weight loss intervention was related to changes of responsiveness to lipolysis in adipose tissue. Various experimental studies in human shown that a short-term (up to 4 weeks) very low calorie diet (VLCD) was able to increase responsiveness of adipose tissue lipolysis to stimulation.[12–14] Similiar to the result, the increment of specific β2-AR induced lipolysis was seen after long-term (8-15 weeks) low calorie diet.[15]

FACTORS THAT INFLUENCE LIPOLYSIS

Because lipolysis has an important role on lipid mobilization, this process is highly regulated. There are some signals with the ability to influence lipolysis by increasing or decreasing the process through several different pathways. Until recently, at least 4 pathways have been investigated.[20] Chaves et al.[20] reviewed that the main pathway that induces lipolysis is the cAMP-dependent protein kinase A (PKA) pathway. Additionally, protein kinase B (PKB), protein kinase C (PKC) pathway, mitogen activated protein kinase (MAPK) pathway, guanylyl cyclise and cyclic guanosine monophosphate (cGMP) were also responsible in regulation on lipolysis.[21–24]

Catecholamines, the SNS signals which includes neurotransmitter norepinephrine and hormone epinephrine, are able to stimulate lipolysis through PKA pathway.[20] When cathecolamine binds to β-AR at the surface of adipocyte, adenylyl cyclise is activated thus intracellular concentration of cAMP increased. Increasing cAMP leads to activation of PKA. Activated PKA intracellular reacts with perilipin 1 and hormone sensitive lipase (HSL) thus leading to activation of those proteins. In non-stimulated condition, HSL is located at the cytoplasm. However, the phosphorilated HSL is able to move to lipid droplet and initiate breakdown of triglyceride.[20] (**Figure 1**)

There are some signals that are also able to induce lipolysis in human adipose tissue. Thyroid-stimulating hormone (TSH) stimulates lipolysis using the same pathway as used

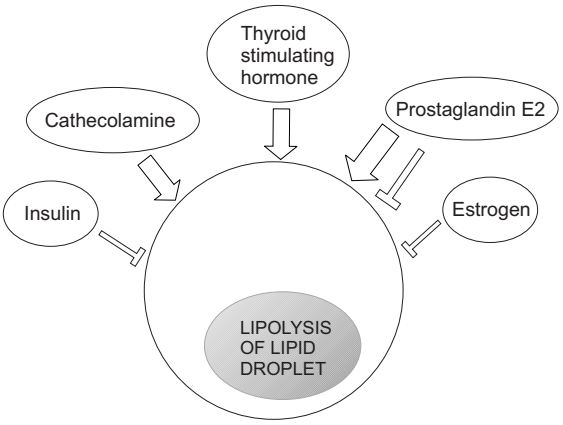

Figure 1. Regulation of adipose tissue lipolysis

by cathecolamines, the PKA pathway. This protein binds to G-protein-coupled receptor inducing stimulation of adenylyl cyclise thus increases cAMP level.[25] Prostaglandin E2 has been reported to affect lipolysis with biphasic effect. Low concentration of Prostaglandin E2 inhibits the response while high concentration of the Prostaglandin E2 leading to stimulatory response.[26,27]

Insulin is secreted by human pancreas and has the ability to inhibit lipolysis through PKB pathway. The signal is firstly recognized by insulin receptors and insulin receptors substrates. Those processes then followed by several reactions mediated by phosphorilation and activation of PDE3B, which decreases cAMP levels. The decreasing level of cAMP thus reduced PKA activity as well as HSL phosporilation. Because less HSL is able to translocate into lipid droplet, less lipolysis occured in the tissue.[20,28] Interestingly, a study done by Campbell et al.[29] revealed that the ability of insulin to suppress lipolysis is impaired in obesity. Location of white adipose tissue in human body is also related to responsiveness to insulin inhibition effect to lipolysis.[30]

ESTROGEN INHIBITS LIPOLYSIS

The relationship between estrogen and adipose tissue metabolism has been investigated before. Low estrogen level in menopause women was associated with loss of subcutaneous fat while male-to-female transsexual receiving estrogen treatment increased subcutaneous fat.[31,32] Additionally, when postmanopause women receiving hormone replacement therapy the epinephrine-stimulated lipolysis was inhibited.[33] In line with the result, estrogen treatment in male-to-female transsexuals was able to inhibit basal lipolysis.[34] Some human experiment studies were done to clarify the acute effect of estrogen to adipose tissue lipolysis. Van Pelt et al.[35] showed that estrogen can acutely reduce basal lipolysis in postmenopause women. Estrogen has also proven to acutely inhibit adrenaline-stimulated lipolysis in abdominal subcutaneous adipose tissue.[36]

Although various studies suggested that lipolysis is inhibited by estrogen signal, mechanism underneath this process is still unclear. Pedersen et al.[37] investigated the influence of estrogen to adrenergic receptors in vivo from estradiol treated women and in vitro. The receptors, including α and β adrenergic receptors, were important proteins that initiate lipolysis in adipose tissue. From those receptors, only α2 adrenergic receptors that is affected by estradiol treatment both in vivo and in vitro.[37] In this study, the response of both subcutaneous and visceral adipose tissue was also evaluated. Interestingly, the effect of estradiol on α2 adrenergic receptors is only seen in subcutaneous adipose tissue.[37] The study showed that adipose tissue LPL and HSL in vivo, the downstream signal of adrenergic receptors, were not affected by estradiol.

Estrogen receptor is a nuclear receptor family of ligand-activated transcription factor that is responsible for physiological action of estrogen. This receptor is divided into 2 subtypes, estrogen receptor α (ER-α) and estrogen receptor β (ER-β). Those subtypes are located in different organs in human body. ER-α is mostly expressed in reproductive tissues, kidney, bone, white adipose tissue, and liver, while ER-β is expressed in the ovary, prostate, lung, gastrointestinal tract, bladder, hematopoietic cells, and the central nervous system (CNS).[38] In order to investigate how estrogen regulate lipolysis, Pedersen et al.[37] also explored which estrogen receptor involved in this process. In the study, they reported that the effect of estrogen to adipose tissue was mediated through ER-α instead of ER-β.[37]

Estrogen could affect cells via genomic

and non-genomic mechanism. The genomic mechanism of estrogen is done via activation of estrogen through direct binding of ER dimmers to estrogen-responsive elements. This process happened in the regulatory regions of estrogen target genes thus transcription of the target genes could start. On the other hand, estrogen could also work through non-genomic mechanism. In this process, activated ERs could activates of several signalling cascade including protein kinase A (PKA), protein kinase C (PKC) and mitogen-activated protein kinase (MAPK).[39]

Investigations have been made to clarify the importance of ER-α in adipose tissue metabolism as well as its role in obesity. In an animal study it was shown that mice lacking of ESR1 gene, a gene that responsible for production of ER-α, have higher amount of adipose tissue compared to wild type.[40] In population based studies, polymorphism of ESR1 gene has been associated with BMI and waist circumferences.[41–45] The genetic expression of ESR1 in subcutaneous adipose tissue has been measured in premenopausal women. Nilsson et al.[43] shown that the expression of ESR1 mRNA was inversely correlated with BMI. However, they found no relationship with variation of that gene with subcutaneous adipocyte lipolysis.

CONCLUSION

Although it has been shown that lipolysis is regulated by estrogen, the mechanism underneath this process is still unclear. Several studies have suggested that this is due to the activation of ER-α but until recently there is no solid evidence to support this hypothesis. Therefore, future study should be aimed to investigate the role of ER-α on lipolysis in adipose tissue. The importance of ER-α signal to affect expression of proteins that are involved in adipose tissue lipolysis should be addressed.

Additionally, investigation on the effect of ER-α agonist to the sensitivity of adrenergic receptor to insulin and norephinephrine is potential to be done in the future. It has been summarized that drugs or treatments targetting on beta adrenergic activation is already approved and used.[8] Thus, new pharmacological and nutritional treatment with ability to modulate ER-α activity/expression could be used as a potential weight loss intervention.

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