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PHYSICAL ACTIVITY AND ADIPOKINES SECRETION IN OBESITY TREATMENT

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Abstract

Obesity is a major epidemiological as well as clinical problem worldwide. It is among the most important reasons of morbidity and mortality in developed countries. Burden of obesity results mainly from disturbed secretory function of adipose tissue. It is currently known that adipose tissue in not merely a storage of energy excess in the form of triglycerides but an important endocrine organ, secreting several biologically active substances named in common adipokines. In obesity secretion of adipokines is disordered. Successful treatment of obesity is not just achievement of weight loss but normalization of metabolism, reduction of other risk factors and restoration of advantageous profile of adipokines. Importance and effectiveness of regular physical activity in antiobesity therapy is unquestionable. It is interesting therefore, to find out how physical activity influences adipokines concentrations. In this review an effort was made to summarize current knowledge about influence of physical activity on adipokines.

Key words: leptin, adiponectin, resistin, exercise, training, obesity, adipokines

Introduction

Obesity is a health problem of epidemic size in the industrialized countries. It has been listed by World Health Organization (WHO) among the chronic diseases of most importance in XXI century.

There are several causes of increasing percentage of the obese people, with decreased physical activity among the most important. Labor-saving technological advances have decreased the physical activity of household chores and workplace tasks, public transportation and widespread car ownership reduced the need of walking. Average daily energy expenditure by means of physical work decreased significantly below the level of 1,75 x basal metabolic rate, recommended by World Health Organization in prevention of obesity (1). Obesity considered itself a chronic disease is connected with increased risk of several pathologies including atherosclerosis, cardiovascular diseases, arterial hypertension, metabolic syndrome, type 2 diabetes mellitus (DM2) and increased risk of carcinogenesis among the most frequent.

Physical inactivity being one of the pathogens of obesity is an important medical problem, taking place among 10 main global reasons of mortality and disability (2). Metabolic syndrome – the state of coexistence of obesity with other morbid disorders, that are important atherogenic cardiovascular risk factors, also develops in most cases in consequence of low physical activity.

The need for effective treatment of obesity is unequivocal. It is obvious that successful therapy of obesity must include caloric intake restriction – diet and increase of energy expenditure in regular physical activity. The latter not only improves the outcomes of short term antiobesity treatment but is also crucial for maintaining the reduced body weight (3,4). Moreover it has been found that regular physical activity improves health outcomes independent of weight reduction (5).

The knowledge of relationships between physical activity and adipokines secretion and action will improve our understanding of mechanisms in which the former exerts its beneficial health effects. Moreover this will help to precise optimal physical activity recommendations.

Endocrine function of adipose tissue in health and obesity

Currently it is known that the burden of obesity is much more than just additional weight load. Since the discovery of adipokines – substances secreted by adipose tissue the latter is not any more considered an inert magazine of energy excess, but an important endocrine organ. The number of currently known adipokines exceeds 50. Among them are substances exclusively secreted by adipose tissue and other, main source of which are different cells and tissues of the organism. Adipokines already identified, having diverse structures, can be classified according to their functional role: appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and hemostasis. It has been postulated that adipose tissue modulates energy metabolism via secretion of circulating adipokines (6).

Obesity is a state of severe disregulation of energy metabolism. It results in disordered metabolic and endocrine function of adipose tissue. Considering the amount of adipose tissue in organism, it becomes clear how significant for the whole body metabolism disturbances of adipokines secretion are. Small adipocytes in lean individuals promote metabolic homeostasis; the enlarged, overgrown, packed with triglycerides adipocytes of obese individuals recruit macrophages and promote inflammation and release of a range of factors that predispose toward insulin resistance (7).

Among the adipokines mainly involved in energy metabolism are: ASP (acylation stimulating protein), leptin, adiponectin, and resistin (8). These are in the focus of interest in this review.

Acylation Stimulating Protein (ASP)

Acylation stimulating protein increases lipogenesis locally in adipocytes by enhancement of fatty acids re-estrifiation and inhibits hormone-sensitive lipase-mediated lipolysis (9). This adipokine stimulates also glucose transport activating diacylglycerol acyltransferase (10). ASP has a primary role in the regulation of lipid metabolism in adipocytes. These actions in adipose tissue result in profound effects on whole-body energy homeostasis and insulin sensitivity. The function of ASP is mainly autocrine and paracrine but may be also considered endocrine (11). ASP secretion by adipocytes in vitro is increased by insulin so probably insulin may also mediate the decrease of ASP production during energy restriction and the increase of ASP production after meal.

Most, but not all studies in humans report substantial increases in plasma ASP in obese subjects (12). Plasma levels of ASP in gynoid obese subjects were found to double these in age matched control subjects (13). Plasma ASP concentrations were observed to decrease during fasting and after weight loss (14, 15).

Adiponectin

Adiponectin, also known as adipoQ or adipocyte complement-related protein Acrp30, is specifically and very highly expressed in adipose tissue. It is a 30 kDa protein that exists in plasma as trimeric, hexameric and higher-order polymeric structures. Adiponectin acts via its specific receptors localized in the skeletal muscle (AdipoR1) and liver (AdipoR2) and directly in blood vessels wall (16). Adiponectin exerts anti-atherogenic, anti-inflammatory and anti-diabetic effects, it stimulates NO synthesis in endothelial cells and improves tissue insulin sensitivity (17-21). Adiponectin serves as an anti-inflammatory molecule in vascular wall as well as in adipose tissue. It also inhibits vascular smooth muscle proliferation, protects endothelium from macrophage adhesion and macrophage-induced injury (22). Adiponectin has anti-inflammatory, anti-atherogenic and antidiabetic properties (23-25). Other important effects of adiponectin are the increase of fatty acid oxidation in peripheral tissues and protection against ectopic fat storage. This adipokine enhances insulin sensitivity in muscle and liver and increases free fat acids (FFA) oxidation in several tissues, including muscle fibers. The recent studies results indicate that rather the high molecular weight (HMW) complexes of adiponectin are associated with beneficial physiologic effects of this adipokine, including increased insulin sensitivity, reduced abdominal fat, and high basal lipid oxidation (26).

It has been found that adiponectin levels are decreased in the states of hyperinsulinaemia (obesity, DM2) and increased in hypoinsulinaemia (diabetes mellitus type 1). Adiponectin concentrations has been observed also to be inversely associated with traditional cardiovascular risk factors, such as blood pressure, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, and are positively related to high-density lipoprotein cholesterol (HDL-C) levels. Low concentrations of adiponectin are connected with accelerated atherosclerosis, coronary heart disease (CHD) and type 2 diabetes mellitus, higher mean systolic and diastolic blood pressure, pathologies well known to be related to obesity (27). The association between adiponectin and insulin resistance was observed also in polycystic ovary syndrome women (28). According to the results of several studies adiponectin levels are negatively associated with visceral and subcutaneous abdominal fat and plasma leptin, and are positively related to the glucose utilization (29).

In humans plasma adiponectin concentrations fall with increasing obesity, and this effect is greater in men than in women. In obesity adiponectin production and secretion are decreased. Obesity decreases also expression levels of AdipoR1/R2 receptors, thereby reducing adiponectin sensitivity, which contributes to insulin resistance (30). Decreased adiponectin secretion is clearly involved in the pathogenesis of metabolic syndrome.

Decreased in obesity adiponectin levels increase significantly after weight loss (31). However it has been observed that very rapid weight loss doesn't cause increase of adiponectin concentration (32). Very interesting is observation that in contrast to obese subjects, caloric restriction with accompanying weight loss in healthy, normal-weight humans may lead to decrease of circulating adiponectin levels (33). It has been found that diet influences adiponectin secretion – adiponectin concentrations appear to be inversely correlated with glycaemic indexes and positively with fiber content of the meals (34).

Leptin

Leptin is probably the best known adipokine. Leptin is product of the ob gene, single-chain pro-

teohormone with a molecular mass of 16 kDa. It is thought to play an important role in the regulation of body energy metabolism. The name leptin originates from the Greek word "leptos", meaning thin. Leptin is produced by differentiated adipocytes, although production of it has been demonstrated in other tissues, such as fundus of the stomach, skeletal muscle, liver, and placenta.

Leptin physiological action is complex. Leptin achieves most of its metabolic effects by interacting with specific receptors located in the central nervous system and in peripheral tissues (35). Central effect of leptin involves suppression of food intake and stimulation of energy expenditure. Leptin, inhibiting food consumption and increasing sympathetic drive, increases metabolic rate and energy dissipation. Insulin and glucocorticoids are stimulators of leptin production, catecholamines via ß receptors suppress it. Sympathetic nervous system activity is believed to be a key inhibitor of leptin release. Catecholamines including norepinephrine, epinephrine and isoprenaline have all been shown directly to inhibit leptin synthesis. Leptin may directly activate sympathetic outflow within the hypothalamus and stimulate adrenal medullary release of epinephrine, thus creating a negative feedback loop between leptin and the sympathetic nervous system.

Leptin receptors belong to cytokine receptor family. Besides the membrane-bound isoforms of leptin receptor, a soluble form of the leptin receptor (sOB-R) has been demonstrated (36). The soluble leptin receptor seems to be extremely important for leptin effects as antiobesity factor. In obese people the fraction of free (unbind to s-OB-R) leptin is increased. Negative correlation between sOB-R and the amount of body fat and a positive one between sOB-R and the WHR has been found (37). In the morbidly obese women who had undergone bariatric surgery during weight reduction, leptin levels decreased, whereas sOB-R levels and the receptor bind fraction of leptin increased (38).

In addition to its metabolic effects, leptin has been shown to have a strong influence on several endocrine axes (39,40). Leptin influence on the development of vasculature (angiogenesis), the production of red blood cells (haematopoesis), immunity and bone formation has also been implicated. Moreover this adipokine is thought to play an important role in normal sexual development and reproduction. Leptin concentrations are higher in female than male and this proportion is unchanged in obesity when the concentrations of leptin in both sexes are increased (41). Leptin secretion is significantly increased in obesity but its expression is also influenced acutely by food intake (42). Although leptin levels are increased in obesity but leptin resistance with decreased levels of soluble leptin receptor develops parallel. In obese subjects, a significantly higher percentage of leptin circulates in the free form compared with lean subjects, and the amount of free leptin increases with BMI, suggesting that leptin-binding proteins are saturated in states of increased adiposity. Even short-term fasting results in an acute and marked decline in total as well as free leptin levels (43). Increased leptin concentration along with increased concentration of soluble leptin receptor occurs in chronic heart failure and is probably responsible for development of cardiac cachexia (44).

Leptin resistance may be main pathophysiological factor for metabolic and cardiovascular dysfunction under obesity. Hiperleptinaemia co-occurring with selective leptin resistance leads to adrenergic hyperactivation observed in obesity (45). Insulin resistance and abdominal obesity are associated with low sOb-R concentration and low bound-free ratio of leptin independent of fat mass. Low sOb-R levels and a low fraction of specifically bound leptin can be considered markers of leptin resistance (46).

Very interesting is an observation made in anorectic patients. In this group decreased leptin levels were correlated inversely with the level of physical activity. That means the lower was leptin concentration the more pronounced was restlessness observed in the patient (47). Other observation, indicating complexity of leptin secretion regulation, is that sleep deprivation decreases plasma levels of leptin in healthy subjects (48).

Resistin

Resistin is the lately discovered adipokine. Resistin belongs to a family of cysteine-rich secretory proteins called resistin-like molecules or FIZZ (found in inflammatory zones) proteins (49). Current data about resisitin and its pathogenetic role are inconsistent. Gender differences in resistin levels have been found (50). Resistin levels in humans were found to be correlated positively with insulin resistance, body mass index and even stronger with fat mass, and negatively correlated with HDL-cholesterol concentrations (51-53). It has been even postulated that resistin induces insulin resistance (54). Observational studies indicate that plasma resistin levels are correlated with markers of inflammation and are predictive of coronary atherosclerosis in humans (55). Resistin stimulates vascular wall smooth muscle cells proliferation so its elevated concentrations increase the risk of atherosclerotic vascular stenosis (56). However in lean subjects without insulin resistance no correlation between BMI and resistin concentration was found (57). Resistin plasma concentrations are increased in obese and also in diabetes mellitus type 2 patients (58). In human the most important source of this adipokine appear to be inflammatory cells of white adipose tissue stroma (59).

Secretory function of adipose tissue in obesity

In obese individuals adipocytes enlarge, adipose tissue undergoes molecular and cellular alterations what affects systemic metabolism, due to the importance of physiologic effects of adipose tissue secreted substances. Increasing amounts of several proinflammatory factors are produced in adipose tissue with growing obesity.

Adiponectin levels are significantly reduced in obese subjects whereas the concentrations of most other adipokines are increased. Changes in secretion and proportions of adipokines occurring in obesity are associated with dangerous metabolism disorders. Reduced adiponectin concentrations as well as increased levels of leptin and interleukin-6 are associated with impaired fibrinolysis in obese hypertensive patients. It has been found that increased leptin concentration in obese individuals with metabolic syndrome is associated with increased number of inflammatory mast cells in adipose tissue (60).

Physical activity in obesity

Regular physical activity is an important measure in health promotion and primary as well as secondary prevention of chronic diseases. This is essential recommendation in obesity treatment. Along with dietary restrictions it enables to achieve negative energy balance. Regular exercise may influence energy balance through an increase in energy expenditure on mechanic work and increasing resting metabolic rate (61). In obese patients, increasing physical activity can enhance fat oxidation, and improve insulin sensitivity.

While it is obvious that physical activity plays a key role in the prevention and therapy of obesity and is therefore, an indispensable component of healthy life style there is still no consensus on what kind and amount of physical activity is optimal (62).

Adipose tissue blood flow increases during exercise, although the increase is not particularly marked except during very prolonged exercise. It appears that there is some minimum value for adipose tissue blood flow at rest in a late postprandial state: blood flow increases as fasting continues, or when a meal is eaten, or during exercise. In all these states, the increase in adipose tissue blood flow may be related to the metabolic activity of the tissue. During fasting or during exercise, adipose tissue releases non-estrified fatty acids (NEFA), and requires a supply of plasma albumin for transport of these NEFA into the circulation. These influences may explain the increased blood flow during fasting or exercise. Studies in patients with spinal cord lesions suggest that circulating catecholamines are more important in the exercise-induced increase in adipose tissue blood flow than sympathetic nerve activity. Obesity is associated with changes in adrenoceptor numbers and subtypes. This suggests that the autonomic signals to adipose tissue are modulated in response to energy stores and adipocyte size.

Exercise training may reduce waist size, independent of changes in BMI, and exercise without weight loss is effective in reducing visceral adipose tissue and preventing further increases in obesity. Exercise may counteract the abnormal metabolic profiles associated with abdominal obesity. It promotes adaptive responses including increase of lipid utilization as the energy source instead of carbohydrate. Even a single bout of exercise can reduce triglyceride levels, increase HDL levels, reduce resting blood pressure, increase glucose tolerance, and reduce insulin resistance. Adding resistance training to aerobic exercise may add to an improvement in insulin sensitivity an increase of muscle mass and resting metabolic rate of this tissue.

It is important to notice that physiological reaction to physical activity is changed in obesity (63,64). Because of this fact it must be remembered that the observations made in lean subjects are not necessary true in obese. Also the response to physical effort in well trained and sedentary subjects is different. This can be the reason of conflicting data from studies performed on different subjects groups.

Physical activity and adipokines

Exercise activates the AMP-activated protein kinase (AMPK) in muscle and other tissues, a pathway that increases fat oxidation and glucose transport. Importantly, the adipocyte hormones: leptin and adiponectin also activate AMPK (65). Activation of AMPK leads to increased fat oxidation and increased glucose transport in muscle. AMPK is currently considered to play key role in maintaining energy balance, both at the single cell and the whole body levels (66). Thus, the adipocyte hormones and exercise act via a similar signal transduction pathway to increase fat oxidation and promote insulin sensitivity. However the relationship between physical exercise and adipokines secretion is unknown.

Only regular physical activity plays role in obesity treatment thus the impact of regular physical training on adipokines concentrations is of most importance. However the effects of single exercise bout are also interesting.

It has been found that exercise influences ASP levels. The impact of single exercise depends upon whether the subject is trained or no. Before training, ASP levels decreased moderately during exercise. Endurance training decreased fasting ASP levels significantly. Interestingly, after 2 weeks of endurance training, ASP levels tended to increase during exercise. Baseline ASP levels was found to correlate negatively with insulin sensitivity both before and after training.

Short-term endurance training reduced baseline ASP levels (67).

Data about impact of physical activity on adiponectin levels are contradictory.

Higher energy intake and lower physical activity independently predict lower adiponectin concentrations (68). Kramer and coworkers investigated acute effects of exercise on circulating adiponectin concentrations. They checked the changes in adiponectin concentrations after moderate intensity exercise in healthy men and strenuous effort in well trained runners. They observed that moderate running protocol (79.0% $\dot{V}O_2$max for 30 min) was associated with a small (10%), but significant, immediate post exercise increase in adiponectin levels, but after correcting for hemoconcentration, the increase was no longer significant. They also found that strenuous intermittent running does not stimulate an increase in production and release of adiponectin. However they discerned moderate increases (23%) in adiponectin after 10 min at 60% $\dot{V}O_2$max, followed by reductions at higher intensities (19.0% reduction after 90 and 100% $\dot{V}O_2$max), and a rebound (11.0%) during recovery. Due to the fact that the changes in adiponectin, paralleled and were not significantly different from the adiponectin changes in the same runners in a resting control trial it was supposed that small increases in adiponectin concentrations resulting from the exercise may be attributed to normal plasma volume shifts. However the authors hypothesized that longer exercise duration would affect adiponectin or more time (longer than 1 h postexercise) may be required for hormonal alterations during exercise to affect the expression of the adiponectin gene (69). Jürimäe et al., investigating an effect of single exercise bout on adiponectin concentration in trained rowers, observed significant decrease immediately after exercise (average decrease from baseline 11%), and supercompensation 30 minutes after exercise (average increase from baseline 20%) (70). Ferguson et al. did not find any change of adiponectin levels in men and women before and immediately after a 60-minute cycle ergometry exercise bout at ~ 65% of $\dot{V}O_2$max (71). Concerning regular training Kriketos et al. found increase of adiponectin plasma concentrations in obese male subjects after 2 -3 bouts of moderate intensity exercises. They observed that increased adiponectin concentrations became first apparent after 1 week of moderately intense training. The 2,5 fold increase of adiponectin levels in obese males following regular exercise training appeared already after three sessions and maintained for 10 weeks of observation (72). In Marcell and coworkers study slight increase of adiponectin concentration after 16 weeks of exercise was insignificant statistically (73).Also Huvler et al., in their study, didn't found influence of exercise training on adiponectin secretion in overweight individuals (average BMI 29 kg/m^2) who had performed endurance exercise training for six months and significantly improved insulin sensitivity without changing body or fat mass. The adiponectin concentration increased in consequence of weight loss. They observed no changes in adiponectin concentration with exercise training that did not alter body mass, despite an improvement in insulin action. In contrast, plasma adiponectin increased in conjunction with insulin action after weight loss. However, what important to notice about this study is, that the first adiponectin concentration assessment was performed after 6 weeks of ramping period when the increase could have already appear (74). Yokoyama et al. didn't observed adiponectin concentration increase in training with moderate intensity diabetic patients (75). On the contrary Yatagai et al. in their study on healthy, normal weight men observed decreased fasting adiponectin concentrations after six weeks of endurance exercise (76). This can be explained by differences of metabolism in slim and obese subjects. Farther information could bring assessment of various molecular weight adiponectin complexes concentration. In study by Brandauer fasting plasma adiponectin levels decreased with endurance, moderate intensity exercise training in men, whereas they remained unchanged in women indicating probable gender differences in reaction to physical activity (77). Fatouros et al. found out that resistance training and detraining may alter leptin and adiponectin responses in an intensity-dependent manner (78).

Influence of physical exercise on leptin concentration has been investigated in several studies. Also the results of experiments monitoring relations between exercise and leptin concentration are conflicting. Number of authors have found that physical activity does not influence plasma leptin. The data from studies evaluating a single exercise session indicate that leptin concentrations can be reduced rather in the days after exercise, if the exercise session meets an energy expenditure threshold, than immediately after the exercise. It seems that short exercise bouts (<60min) do not influence leptin secretion unless they are extremely intensive – to exhaustion. Probable are increases during exercise followed by decreases after the exercise. It seems that negative energy balance is necessary to decrease leptin concentration. Long-term (>60 min) exercise effects on leptin, a reduction in leptin concentrations also depends on energy balance. Very long bouts of exercise are more likely to reduce leptin levels, which is probably due to disruption of energy balance. Regular exercise training effects are even less clear. Short term exercise training seems not to affect leptin secretion. Information about effect of longer exercise training >12 weeks are discordant. Some studies found only leptin reductions associated

with reduction of adiposity other indicate that there is possible reduction of leptin concentration after training, independent from fat loss (79,80). Athletes trained in aerobics have reduced level of plasma leptin in the result of reduced body fat (81). There are several factors besides exercise that are supposed to influence plasma leptin concentration among them: food, food composition, ambient temperature, sleep pattern and recent net energy balance. Jürimäe et al. found out that even short bout of intensive exercise in trained athletes-rowers results in decrease of leptin concentration if it engages all large muscle groups (82). In very interesting study performed on large number of subjects Franks et al. found that independent of obesity and other confounding factors, leptin level and physical activity energy expenditure are inversely related. The authors hypothesized that physical activity modifies a number of mechanisms underlying leptin action, such as sympathetic nervous stimulation (83).

In several studies it was found that physical activity causes decrease of leptin concentration when it is connected with sufficient energy expenditure (84,85). Interesting is an observation that a daily fish meal as part of a weight-reducing regimen was more effective than any other weight reducing diet at reducing leptin levels (86).

Resistin is the least known adipokine. Also association between physical activity and resistin concentration hasn't been investigated so widely. In few studies yet concerned to the influence of physical activity on resistin concentrations no such impact has been found (87,88).

Secretion of adipocytokines by adipose tissue appears to depend upon several factors: the size of the triglyceride stores, recent wholebody energy balance and insulin/glucose signals, and other 'descending' influences from the sympathetic nervous system and other endocrine systems such as hypothalamo-pitui-

Table 1. *Adipokines serum concentrations and physical exercise in athletes and untrained people (92)*

ASP			
One exercise bout		Systematic training	
Untrained people	Athletes	Untrained people	**Athletes**
Decrease (82)	- Increase (82)	- Decrease (82)	-
ADIPONECTIN			
One exercise bout		Systematic training	
Untrained people	Athletes	Untrained people	**Athletes**
- No changes (93) - Increase only due to hemoconcentration (69)	- Transitory decrease (69) - No changes (69,106) - Initially no changes increase 30 minutes after termination of exercise (70)	- Transitory decrease (76) - No changes (74,75) - Increase after two weeks of training in obese males (72) - No changes in moderate training with higher intensity increase of concentration (73)	- In female athletes higher than in general population extremely high in amenorrheic female athletes (94)
LEPTIN			
One exercise bout		Systematic training	
Untrained people	Athletes	Untrained people	Athletes
- No changes (71,95) - Decrease when exercise fasting (96) - Decrease after exhaustive exercise (82)	- Transitory increase (97) - Decrease after maximal exercise (82)	- Decrease (98,99) - Only changes due to body mass reduction (79) - Concentrations negatively correlated with physical activity energy expenditure (83)	- No changes after increasing training loads (100) - Lower in trained athletes (81)
RESISTIN			
One exercise bout		Systematic training	
Untrained people	Athletes	Untrained people	Athletes
No data	No data	No changes in obese type 2 diabetics (87)	No data

tary axis and growth hormone axis (89). For example changes of adiponectin and leptin concentration depend upon the training status as was proved in Jürimäe et al. study (90). In study by Monzillo weight reduction in obese individuals with insulin resistance achieved by caloric restriction and moderate exercise training (150 min/week 60-80 min maximal heart rate) was associated with a significant decrease in leptin, whereas adiponectin was increased only in diabetic subjects (91).

The current information doesn't explain the relationship between physical activity level and adipokines secretion and action. Lot of study is necessary to clear out how physical activity influences adipose tissue secretory function. This knowledge will allow developing precise and comprehensive physical activity recommendations for normal and obese subjects. In the review above most interest was concerned to the role of physical activity in obesity prevention and treatment. It is worthy however to be mentioned that thorough knowledge of adipokines-physical activity interrelationships may be also useful in prevention female athlete's syndrome. The need to understand the effects of physical activity on various metabolic processes adipokines secretion and function among them is current research problem.

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