White adipose tissue (WAT) is now recognized as a highly active metabolic tissue and important endocrine organ producing numerous peptides and proteins with broad biological activity. The term “adipokines” has been coined to refer to a series of adipocyte-derived biologically active molecules, which may influence the function as well as the structural integrity of other tissues. Adipokines are implicated in control of food intake, energy balance and body weight (leptin), glucose homeostasis (e.g., adiponectin, resistin, adiponutrin), lipid metabolism (e.g., retinol-binding protein, cholesteroleser transfer protein), angiogenesis (vascular endothelial growth factor VEGF), fibrinolytic system (plasminogen activator inhibitor-1 PAI-1), pro- and anti-inflammatory effects (e.g., tumor necrosis factor-α TNF-α, interleukin-6 IL-6) or sexual development and reproduction (leptin). Alterations of WAT mass in obesity or lipoatrophy effect the production of most adipose secreted factors.

Besides others, alcohol consumption affects also hormonal system leading to non-physiological increase/decrease of hormone gene expression and plasma hormone concentrations appearing as final poor or stronger effects on target tissues. As mentioned above, white adipose tissue is important endocrine organ, so alcohol intake can alter also adipokines expression in WAT and adipokines plasma levels and in this way it can affect the adipokine-targeted tissues and their functions.

Key words: Adipokines – Adiponectin – Adiponutrin – Alcohol – Fat tissue – Leptin – Resistin – Visfatin

For a long time it was believed that white adipose tissue functioned only as a passive site of energy storage, heat isolation and mechanical cushion. Recent studies clearly demonstrate that WAT is an important endocrine organ producing numerous peptides and proteins with broad biological activity. Secretory products of WAT are collectively called adipokines and up to the present it has been identified more than 50 adipokines with various autocrine, paracrine and endocrine functions. They are implicated in glucose homeostasis (e.g., adiponectin, resistin, adiponutrin), lipid metabolism (e.g., retinol-binding protein, cholesteroleser transfer protein), angiogenesis (vascular endothelial growth factor VEGF), fibrinolytic system (plasminogen activator inhibitor-1 PAI-1) or pro- and anti-inflammatory effects (e.g., tumor necrosis factor-α TNF-α, interleukin-6 IL-6). Brief overview of most important adipose is shown in Table 1.

As a secretory tissue, WAT displays several unusual characteristics. First, instead of being confined at a specific location, WAT is found throughout the whole organism in individual pads that are not physically connected. According to the WAT location we can recognize several types of WAT, for example retroperitoneal, epididymal, subcutaneous, mesenteric, pericardial fat pads. Second, WAT is constituted of distinct cell types, including mature adipocytes, pre-adipocytes, fibroblasts and macrophages, all of which participate, to a greater or lesser extent, in WAT secretory function. For example, differentiation of pre-adipocytes into mature adipocytes was necessary to induce 64-fold increasing expression of adiponectin in a human adipocyte cell culture model (Körner et al. 2005). Third, individual adipose tissue pads are heterogeneous in the extent of metabolic activity, depending upon localization of fat depot, e.g. visceral vs. subcutaneous fat.
Similarly, certain depots might contribute more actively than others to the production of specific adipokines (Fried et al. 1998, Dusserre et al. 2000). Leptin mRNA is quantitatively expressed in a depot-specific manner, in the following order: retroperitoneal = epididymal > mesenteric > subcutaneous (Villafuerte et al. 2000). Fourth, some adipokines are also secreted by non-adipose tissues. Morash et al. (2003) reported that resistin is not exclusively synthesized in adipocytes, since resistin mRNA is also observed in mouse brain and pituitary. In humans, in addition to WAT, resistin has also been found in monocytes (Nagaev and Smith 2001; Savage et al. 2001) and placenta (Yura et al. 2003). Finally, little is known regarding the molecular mechanisms involved in the biosynthesis and exocytosis of adipokines (Guerrero-Millo 2004).

Alcohol consumption interferes with the nutritional status of the drinker. For example, alcohol can alter the intake of food, and absorption and utilization of various nutrients into the body. Alcoholic beverages primarily consist of water, pure alcohol and variable amounts of sugars. Therefore, any calories provided by alcoholic beverages are derived from the carbohydrates and alcohol they contain. Pure alcohol provides approximately 7.1 kilocalories per gram. Because they provide almost no nutrients, alcoholic beverages are considered “empty calories” (Lieber 2003). Final effect of alcohol intake on human health depends on several factors such as:

* Amount and regularity of consumed alcohol. For example, for moderate drinkers, alcohol does not suppress food intake and may actually increase appetite. Chronic consumption appears to have the opposite effect. Alcohol causes euphoria, which depresses appetite, so heavy drinkers tend to eat poorly and become malnourished.

* Amount and composition of food. Alcohol drink after a meal is absorbed about three times more slowly than on empty stomach (Jones and Jönnson 1994).

* Gender. Women have in comparison with men smaller amount of total body water and lower activity of alcohol dehydrogenase enzyme in the stomach, causing a larger proportion of the ingested alcohol to reach the blood (Saunders et al. 1981, Frieza et al. 1990).

* Smoking or other drugs. The stimulatory effects of alcohol, nicotine and cocaine on cellular expression and release of endogenous morphine suggest convergent mechanisms underlying the reinforcing and addictive properties for a variety of drugs of abuse (Zhu et al. 2006).

* Genetic predisposition. Microarray analyses of brain gene expression in mice (several strains that show a high or low degree of alcohol preference) led to iden-

---

### Table 1

<table>
<thead>
<tr>
<th>Adipokines levels and their relations to metabolic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obesity</strong></td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Leptin</td>
</tr>
<tr>
<td>Adiponectin</td>
</tr>
<tr>
<td>Resistin</td>
</tr>
<tr>
<td>Adiponutrin</td>
</tr>
<tr>
<td>Visfatin</td>
</tr>
<tr>
<td>BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TGC = triacylglycerols</td>
</tr>
</tbody>
</table>
tification of 20 candidate genes as regulators of alcohol preference that include some genes of unknown function (Mulkigan et al. 2006).

Immoderate alcohol intake exerts some harmful effects itself or through its metabolic breakdown proceeding particularly in the liver. Both cytosolic enzymes, alcohol dehydrogenase (ADH) and microsomal cytochrome P450 system (MEOS), generate toxic products such as acetaldehyde, and highly reactive and potentially damaging oxygen-containing molecules, evoking oxidative stress (Lieber 1992, 2000). Hyperlipidemia and accumulation of fat in the liver are the most common disturbances of lipid metabolism produced by alcohol, leading to genesis of fatty liver, alcoholic hepatitis and in the last phase to alcoholic cirrhosis. ADH way of alcohol metabolism generates excess amounts of reduced form of nicotinamide adenine dinucleotide NADH. In the liver the increased NADH/NAD ratio favors esterification of fatty acids in the liver, synthesis of cholesterol and fatty acids and decreases fatty acids oxidation and hydrolysis by hepatic mitochondria. Moreover, lesser availability of NAD diminishes citric acid cycle activity (Baraona and Lieber 1979). Alcohol intake is the second fundamental cause of hyperlipidemia in the population after diabetes mellitus. Accumulation of lipids in the blood occurs when their rate of entry into the blood exceeds their rate of removal. Thus, hyperlipidemia can be produced either by an excessive production and release of lipids into circulation or by defective removal from the blood or by combination of these mechanisms (Baraona and Lieber 1979).

However, moderate alcohol consumption is associated with some beneficial and helpful consequences. Most of the benefit of alcohol appears to be related with a reduction in atherosclerotic cardiovascular disease risk. Moderate alcohol consumption, defined as 1 to 3 drinks daily, compared with abstinence is associated with a 30%-60% reduction in coronary heart disease risk (Moore and Pearson 1986). Protective effect of alcohol on the incidence of stroke has been found with moderate consumption. Stroke incidence increases with consumption above 4 drinks daily, predominantly because of increased intracerebral and subarachnoid hemorrhage (Goldberg et al. 2001). Most of profitable effects of alcohol are due to increases in high-density lipoprotein (HDL) cholesterol (Gaziano et al. 1993; De Oliveira et al. 2000). Two drinks daily increase HDL cholesterol 10% to 15% (Gaziano et al. 1993). The increase in HDL cholesterol results from an increased production of apo A-I and apo A-II, the precursors of HDL, without a change in HDL catabolism (De Oliveira et al. 2000). Many prospective studies suggest that light to moderate drinking may protect against the development of diabetes (Mayer et al. 1993; Kiechl et al. 1996). This is consistent with observations that low to moderate amounts of alcohol intake increase insulin sensitivity (Lazarus et al. 1997).

Alcohol consumption also affects hormonal system leading to non-physiological increase/decrease of hormone gene expression and plasma concentrations appearing as final poor or stronger effects on target tissues. For example, in the adrenal cortex alcohol directly or indirectly by adrenocorticotropic hormone (ACTH) increases production of cortisol (Rivier et al. 1984). Effect of alcohol consumption on increased growth hormone levels was demonstrated in both animals and human (Emanuele et al. 1992). As mentioned above, white adipose tissue is an important endocrine organ, so alcohol intake can alter also adipokines expression in WAT and adipokines plasma levels. The aim of this review is summarize the present knowledge about the effect of alcohol on leptin, adiponectin, resistin, adiponutrin and visfatin.

Adipose tissue is an endocrine active organ

Leptin. Leptin first described in 1994 (Zhang et al. 1994) links adipose stores with hypothalamic centers and is considered as one of the main peripheral endocrine signals involved in the regulation of food intake and body weight (Campfield et al. 1995; Hallas et al. 1995). Leptin, the hormone encoded by the obesity (ob) gene (Zhang et al. 1994), is a 16-kDa protein made up of 167 aminoacids (Ahima et al. 2000). Except of adipose tissue other sources of leptin are also hypothalamus (Morash et al. 1998), pituitary (Jin et al. 2000), skeletal muscle (Wang et al. 1998), stomach (Bado et al. 1998), placenta (Hoggard et al. 1997), mammary epithelium (Smith-Kirwin et al. 1998) and testes (Friedman 1998), where leptin may have local paracrine function. Leptin receptors (OB-R) have been identified in the hypothalamus, gonadotrope cells of the anterior pituitary (Jin et al. 2000), granulose, theca and interstitial cells of the ovary (Karlsén et al. 1997), endometrium (Kitawaki et al. 2000), and Leydig cells (Caprio et al. 1999). Alternative splicing of the leptin receptor mRNA results in at least six isoforms of OB-R (Tartaglia 1997). One of them, the long form (OB-Rₐ) is highly expressed in the hypothalamus and is crucial for leptin action in the central nervous system (Elm-
The function of the short isoform (OB-Rs), which is expressed in a more widespread fashion in peripheral tissues, is less clear, and may mediate leptin clearance or leptin transport through the blood-brain barrier (Banks et al. 1996; Biorbaek et al. 1997).

In particular, it has been found that leptin decreases appetite and reduces the massive obesity of leptin-deficient (ob/ob) mice, and that the concentration of leptin in the blood (in the fed state) varies with the amount of adipose tissue in the body (Campfield et al. 1996; Vernon and Houseknecht 2000). Leptin exerts its anorexigenic effects in central nervous system through several neuroendocrine systems, including the hypothalamus-pituitary-adrenocortical (HPA) axis (Uehara et al. 1998). Leptin enters the brain by way of a saturable transport system located at both the endothelium and choroid plexus (Banks et al. 1996, Zlokovic et al. 2000). In basomedial hypothalamic leptin binds to leptin receptors (OB-Rs) in arcuate (ARC), dorsomedial hypothalamic (DMH) and ventromedial hypothalamic (VMH) nuclei (Elmoquist et al. 1998, Baskin et al. 1999b). In arcuate neurons co-expressing OB-Rs and pro-opiomelanocortin (POMC), leptin increases POMC production, which generates an anorexigenic (appetite-suppressing, promoting satiety) signals such as β-melanocyte-stimulating hormone (β-MSH), and also cocaine and amphetamine regulated transcript (CART) (Schwartz et al. 1997; Elias et al. 1998; Kristensen et al. 1998). In neurons that express OB-R1, neuropeptide Y (NPY) and agouti-related peptide (AgRP), leptin inhibits expression of both NPY and AgRP, both potent stimulators of food intake (Schwartz et al. 1996; Hahn et al. 1998; Baskin et al. 1999a). Leptin action in ARC results in inhibition of food intake, increased brown fat thermogenesis and thus contributes to reduction of adipose tissue mass (Stephens et al. 1995). Disturbed equilibrium between the anorexigenic and orexigenic factors manifests as food intake disorders, increase in body weight and obesity or decrease in body weight, i.e. cachexia (Stasiuniene and Praskevicius 2005).

Leptin also acts in the hippocampus where it facilitates the induction of long-term potentiation and enhances N-methyl-D-aspartate (NMDA) receptor-mediated transmission. This suggests that leptin plays a role in learning and memory. Obese mice and rats, which have leptin receptor deficiency, have impaired spatial learning (Farr et al. 2006).

Leptin expression and adipocytes secretion is influenced by insulin, glucocorticoids, estrogens and cytokines, including TNF-α and interleukin-1, which stimulate leptin secretion (De Vos et al. 1995, Machinal et al. 1995). On the contrary, fasting, sympathetic nervous activity via catecholamines, androgens and agonists of peroxisome proliferator-activated receptor (PPAR) inhibit leptin secretion (Wabitsch et al. 1997, Friedman and Halaas 1998; Ahima et al. 2000). At now, there is an evidence that leptin may be independently involved in insulin secretion and action besides its effects on food intake and body weight regulation (Yildiz and Haznedaroğlu 2005). Circulating glucose and insulin levels appear to have a stimulatory effect on leptin secretion (Sonnenberg et al. 2001). On the other hand, increased plasma leptin levels act to increase peripheral insulin sensitivity while reducing insulin release from pancreatic beta cells. This bidirectional feedback loop between adipose tissue and pancreatic islets is called “adipoinsular axis” (Kieffer and Habener 2000).

Under physiological conditions, the amount of circulating leptin is directly correlated with both body mass index and total body-fat mass. Hence, obese individuals have elevated circulating leptin levels that fail to mediate weight loss indicating a form of leptin resistance in most human obesity (Bates and Myers 2003).

**Adiponectin.** Adiponectin is a 29-kDa protein exclusively expressed and secreted by adipose tissue, which displays several antitherogenic, anti-diabetogenic and anti-inflammatory effects. In target tissues (skeletal muscle, liver, pancreatic β-cells, brain) (Kharroubi et al. 2003; Yamaguchi et al. 2003), it is an antagonist of TNF-α (Brunt 2001, Fruebis 2001, Li 2003). Adiponectin inhibits the production of glucose in the liver, enhances lipoprotein clearance and increases beta-oxidation of fatty acids (Shapiro and Scherer 1998; Hotta et al. 2001; Berg et al. 2002).

Contrary to other adipokines, which are markedly up-regulated in obesity, adiponectin expression in adipose tissue and circulating levels are found to be lower in obese subjects than in lean subjects in human and animal models of obesity and type 2 diabetes (Hotta et al. 2000; Yamaguchi et al. 2001). Adiponectin plasma levels have been reported to strongly correlate inversely with body mass index (BMI) (Arita et al. 1999, Yang et al. 2002), percent of body fat (Weyer et al. 2001; Stefan et al. 2002a), muscle lipid content (Weiss et al. 2003) and waist-to-hip ratio both in humans and in animals (Stefan et al. 2002b; CNop et al. 2003). Furthermore, plasma adiponectin is negatively correlated with plasma triacylglycerides, low-density lipoprotein cholesterol and positively correlated with high-density lipoprotein cholesterol (Yamamoto et al. 2002; CNop
Adiponectin levels are reduced in patients with cardiovascular disease (Ouchi et al. 1999) and in diabetics (Hotta et al. 2000). Results of epidemiological studies suppose that low levels of adiponectin could predict the later development of type 2 diabetes (Lindsay et al. 2002; Spranger et al. 2003), and myocardial infarction (Nakamura et al. 2004; Pischon et al. 2004).

Studies with hyperinsulinemic-euglycemic clamp (Hotta et al. 2001, Weyer et al. 2001) and other studies (CNop et al. 2003) have revealed that a high level of adiponectin is closely related to increased insulin sensitivity. Adiponectin has been shown to increase insulin sensitivity by increasing fatty acid oxidation in skeletal muscle, which results in decreased accumulation of triacylglycerides, a key factor for progressing of insulin sensitivity (Fruhbis et al. 2001; Yamachi et al. 2002). Moreover, it is demonstrated that adiponectin administration decreases plasma glucose and non-esterified fatty acid levels (Fruhbis et al. 2001; Combs et al. 2002). All these factors lead to an improvement in glucose tolerance and to a reduction in insulin resistance, which can be observed when treating insulin-resistant mice with physiological doses of adiponectin (Yamauchi et al. 2001). The basis of molecular mechanism of insulin-sensitizing effect by adiponectin is activation of 5'-AMP-activated protein kinase (AMPK) in the muscle and liver (Hardie et al. 1998; Arita et al. 1999). Stimulation of AMPK results in increase fatty acid oxidation (Winder and Hardie 1999) and glucose uptake in skeletal muscle (Mu et al. 2001). Moreover, activation of AMPK reduces expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), the key enzymes of gluconeogenesis (Ouchi et al. 1999). It has been recently shown that adiponectin not only improves insulin sensitivity but also augments glucose-stimulated insulin secretion (Winzell et al. 2004). The above-described properties indicate that dysregulation of adiponectin expression and its plasma concentration may be relevant to the development of insulin resistance (Ouchi et al. 1999).

**Resistin.** Resistin is a recently discovered adipokine secreted by rodent adipocytes. It was first described as a hormonal signal involved in the induction of the insulin resistance associated obesity (Steppan et al. 2001). This 12.5-kDa cysteine-rich polypeptide is mainly secreted by white adipose tissue with the highest levels in female gonadal adipose tissue (Steppan and Lazar 2002). A scan of a variety of human tissues by RT-qPCR showed that the highest expression of human resistin gene is in bone marrow followed by lung with almost undetectable levels in adipose tissue (Patel et al. 2003). Curat et al. (2006) have shown that in human visceral adipose tissue resistin was predominantly produced and released by the nonfat cells of adipose depots - from WAT-derived macrophages. Additionally, human resistin has been detected in human placental tissue, mainly in trophoblastic cells (Yura et al. 2003).

Rodents resistin serum levels were increased in obesity and resistin gene expression was induced during adipocyte differentiation. In addition, administration of resistin impaired glucose tolerance and insulin action while neutralisation of resistin reduced hyperglycemia in the mouse model of diet-induced insulin resistance (Steppan et al. 2001). Recent reports have also indicated that resistin impairs insulin action on hepatic glucose production, inhibits insulin-stimulated glucose uptake in skeletal muscle and adipocytes independent of glucose transporter GLUT-4 (Moon et al. 2003; Rajala et al. 2003) and suppresses glucose uptake in hepatocytes (Steppan et al. 2001). The adipocyte-derived resistin is therefore regarded as a link between obesity and insulin resistance (Steppan and Lazar 2004). Accordingly, elevated serum resistin concentrations have been found in obese individuals and patients with diabetes mellitus (McTernan et al. 2003; Youn et al. 2004).

However, the physiological relevance of resistin in man is under debate. While in rodents resistin appears to have an important role in the development of liver insulin resistance, its role in humans is less clear and it is probably involved in the regulation of inflammatory processes rather than in insulin sensitivity (Haluzik and Haluzikova 2006). Furthermore, recent study identified serum resistin as a powerful diagnostic marker to assess the severity of liver disease (liver cirrhosis) and patients with typical clinical complications (Yagmur et al. 2006).

**Adiponutrin.** Adiponutrin is one of three recently identified adipocyte lipases, which is expressed exclusively in adipose tissue (Baulande et al. 2001). Although adiponutrin is membrane-bound and non-secreted 48-kDa protein, it does show features characteristic of many of the adipose-specific adipokines. In rodents, its gene expression is regulated by changes in nutrition and energy balance. The adiponutrin gene is downregulated by fasting and upregulated by refeeding or feeding with a high-carbohydrate diet, suggesting a role in lipogenesis (Baulande et al. 2001; Polson and Thompson 2003). Johansson et al. (2006) have identified two adiponutrin gene polymorphisms associated with obesity. They have presented that obese subjects that are
insulin resistant and/or carriers of obesity-associated adiponutrin gene alleles fail to upregulate the gene. This upregulation of adiponutrin may be an appropriate response to arrange energy excess. The study on non-obese and obese women has shown no differences in adiponutrin mRNA levels. However, low calorie diet reduced the average level of adiponutrin mRNA expression by 36%, whereas refeeding elevated the mRNA level by 31%. Even the mRNA level of adiponutrin was negatively correlated with fasting glucose and subjects with high adiponutrin mRNA level had increased insulin sensitivity. Compared with other adipocytes proteins such as leptin and adiponectin, adiponutrin mRNA did not show correlation with either adiposity indexes or with leptin and adiponectin mRNAs (LIU et al. 2004).

Visfatin. Visfatin is a recently identified adipokine, which was named because of its much more expression in visceral adipose tissue than in subcutaneous fat (ASSAL et al. 2005). Both, its tissue expression and plasma levels increase in parallel with obesity (SÉTHI and VIDAL-PUG 2005). Since high-fat diet increases plasma visfatin, it is possible that it has an important role in diet- or obesity-induced insulin resistance. Plasma visfatin correlates with visceral fat in human subjects suggesting that it may be a useful target for the development of drug therapies for diabetes (FUKUHARA et al. 2005). Visfatin binds to the insulin receptor and induces its autophosphorylation, as well as phosphorylation of a number of downstream products consistent with induction of the insulin/insulin receptor signal transduction pathway. It does not bind to the same segment of the insulin receptor as insulin (FUKUHARA et al. 2005). This new adipocytokine exerted insulin-mimetic effects that were dose-dependent and quantitatively similar to those of insulin (ASSAL et al. 2005). In vitro, visfatin had several insulin-like actions including enhancement of glucose uptake, suppression of glucose release, accumulation of triacylglycerides, and induction of gene markers of adipocyte differentiation (PPARγ, fatty acid synthase, adiponectin).

Effect of alcohol on adipokines

Leptin. Most of studies investigating the effect of alcohol intake on leptin levels have shown increased circulating leptin concentrations compared with abstinent controls both in humans and animals (OBRADOVIC and MEADOWS 2002). Circulating leptin levels increased in a dose-dependent manner in chronic alcoholism, regardless of nutritional status or the presence of compensated liver disease (NICOLAS et al. 2001). Also ROTH et al. (2003) have established increased serum leptin levels in postmenopausal women after moderate alcohol intake (15-30 g of alcohol/day), which may be responsible for morbidities associated with chronic elevations of this hormone such as breast cancer. In alcohol-drinking normal rats serum leptin concentration was found to be augmented despite reduced blood insulin (SZKUDELSKI et al. 2004). Since under physiological conditions leptin secretion is potentiated by insulin (SALADIN et al. 1995), these results indicate that after alcohol consumption physiological mechanisms regulating leptin secretion is disturbed.

However, some literature data also demonstrate decrease or no change of leptin levels after alcohol intake. In healthy subjects acute alcohol ingestion (0.45 g/kg body weight) declined the serum leptin levels, but did not change secretion of insulin or IGF-1 (insulin-like growth hormone-1) (CALISSENDORFF et al. 2004). ŠTRBAK et al. (1998) have reported that decrease of solid food intake during four-week alcohol consumption in pubertal rats was not due to an increase of plasma leptin in spite of significantly lower body mass gain. Comparison between changes in leptin levels induced by fasting and dietary fat restriction has shown that plasma leptin levels primary reflect total adipose mass, rather than meal consumption or dietary energy source (WEIGLE et al. 1997). MIKOLAICZAK et al. (2002) have studied the effect of 5-week voluntary alcohol consumption on plasma and cerebrospinal fluid (CSF) leptin levels in adult male Warsaw high alcohol preferring (WHP) and low preferring (WLP) rats. In WLP rats plasma and CSF leptin levels were significantly elevated, however, WHP animal plasma leptin concentration was unchanged and CSF leptin level was reduced.

Up to now, we do not have clear and unambiguous explanations about how the consumption of alcohol influences leptin level. The above discrepancies may result from different experimental settings of particular studies such as various subjects (humans vs. animals), animal strains (Wistar rats, WHP and WLP rats, Sprague-Dawley rats), gender, food composition, manner of alcohol feeding (i.p., i.g. administration, liquid diet supplement), alcohol doses, duration of treatment (acute, chronic).

Moreover, in the hypothalamus and peripheral adipose tissue chronic alcohol consumption has also altered expression of molecules involved in leptin signalling pathway such as leptin receptor or some post-receptor signal transducers and activators of transcription (OBRADOVIC and MEADOWS 2002). In the hypothalamus and the perigonadal fat of mice consuming 20%
(w/v) alcohol during 5 weeks the overall expression of leptin receptors was increased while the expression of the physiologically active long form of leptin receptor (OB-R) was decreased. In 293 cells expressing OB-R, alcohol inhibited the tyrosine phosphorylation of leptin receptor (Degawa-Yamauchi et al. 2002). The effects of alcohol on transcriptional factors STAT, which are after activation of OB-R phosphorylated by kinase from Jak family, are different. Hypothalamic expression of transcription factor STAT3 was decreased after alcohol intake (Obradowic and Meadows 2002). In contrast, STAT1, transcription factor associated with leptin receptor activation in adipose tissue, was significantly elevated in the perigonadal fat of alcohol-consuming mice compared with water-consuming control animals (Obradowic and Meadows 2002). In vitro study with Huh7 cells (human hepatoma cell line) demonstrated, that leptin-induced STAT3 phosphorylation was dose- and time-dependently inhibited by pretreatment with alcohol. Alcohol has no effect on the amount of STAT3 protein or leptin-induced JAK2 phosphorylation. It is possible that p38 mitogen-activated protein kinase (MAPK) may play the leading role in this inhibition. It is understood (HOTAMISLIGIL et al. 1993). One hypothesis is based on increased circulating adiponectin levels observed with moderate alcohol consumption. Possible mechanism supposes that increased adiponectin in plasma may cause a decrease of tumor necrosis factor-α levels, which has direct effects on tyrosine phosphorylation of the skeletal insulin receptors. High levels of TNF-α have long been implicated to cause high basal phosphorylation of the insulin receptors in muscle by tyrosine kinase (HOTAMISLIGIL et al. 1994) with the consequence of insulin resistance (HOTAMISLIGIL et al. 1993, HOTAMISLIGIL et al. 1995). In vitro studies showed that adiponectin reduced both TNF-α production and TNF-α-induced biological effects (Ouchi et al. 1999; Ouchi et al. 2000; Yokota et al. 2000). The three-dimensional structure of adiponectin closely resembles that of TNF-α (Shapiro and Scherer 1998) and these two proteins have completely opposite effects. Both in vivo and in vitro experiments demonstrated that adiponectin and TNF-α suppress each other’s production and also antagonize each other’s action in their target tissues (Mae-da et al. 2002).

Adiponectin. The mechanism of increased insulin sensitivity in moderate alcohol consumers is not well understood (Hotamisligil et al. 1993). One hypothesis is based on increased circulating adiponectin levels observed with moderate alcohol consumption. Possible mechanism supposes that increased adiponectin in plasma may cause a decrease of tumor necrosis factor-α levels, which has direct effects on tyrosine phosphorylation of the skeletal insulin receptors. High levels of TNF-α have long been implicated to cause high basal phosphorylation of the insulin receptors in muscle by tyrosine kinase (Hotamisligil et al. 1994) with the consequence of insulin resistance (Hotamisligil et al. 1993, Hotamisligil et al. 1995). In vitro studies showed that adiponectin reduced both TNF-α production and TNF-α-induced biological effects (Ouchi et al. 1999; Ouchi et al. 2000; Yokota et al. 2000). The three-dimensional structure of adiponectin closely resembles that of TNF-α (Shapiro and Scherer 1998) and these two proteins have completely opposite effects. Both in vivo and in vitro experiments demonstrated that adiponectin and TNF-α suppress each other’s production and also antagonize each other’s action in their target tissues (Mae-da et al. 2002).

Sierksma et al. (2004) reported that moderate dose of alcohol with dinner in healthy middle-aged men is associated with a significant increase in plasma adiponectin without changes in plasma TNF-α. In a small group of insulin-resistant middle-aged men they observed increased adiponectin serum levels and a borderline significant increase in insulin sensitivity after moderate alcohol consumption. However, the correlations between plasma adiponectin and TNF-α level and
between plasma TNF-α level and insulin sensitivity index (ISI) were not statistically significant. Circulating TNF-α might not represent activity at the tissue level. KERN et al. (2001) pointed out the strongest association between insulin resistance and adipose-secreted component of TNF rather than with plasma TNF-α, suggesting a paracrine function of TNF-α in adipose tissue.

Another evidence that alcohol may modulate the inhibitory effect of TNF-α on adiponectin production and thus, increase its plasma concentrations originates from study of STEJSKAL et al. (2005). Whereas drinkers suffering from liver steatosis were found to have a positive correlation between adiponectin concentrations and TNF-α, such correlation was absent in non-drinkers suffering from the similar hepatopathy.

BEULENS et al. (2006) have also demonstrated that in healthy middle-aged men after 28 days of daily consumption 450 ml of red wine (40 grams of alcohol) plasma adiponectin concentrations significantly increased (p<0.01) compared with consumption of dealkoholized red wine. The correlation between changes in plasma adiponectin and ISI was not present.

The similar study was also performed in a large heterogeneous group of nondiabetic subjects with or without family history of type 2 diabetes (THAMER et al. 2004). In group without alcohol consumption insulin sensitivity was significantly lower compared to subjects consuming alcohol only occasionally, 2-3 days a week or more than 5 days a week. The observed heterogeneous group included both men and women; however, it is known that women have about 40% higher circulating levels of adiponectin than men (ARITA et al. 1999). The level of androgens may play a role for these gender differences because androgens appear to have gender differences because androgens appear to have an inhibitory effect on adiponectin secretion and plasma concentrations (NISHIZAWA et al. 2002). Because of sex differences in alcohol metabolism (CHROSTEK et al. 2003) and in adiponectin serum levels (TSCHRITTER et al. 2003), the relationship between alcohol consumption and adiponectin level was analyzed also separately in men and women. In both groups abstinent subjects were found to have significantly lower adiponectin serum concentrations than subjects consuming alcohol (THAMER et al. 2004).

In our experiments adult Wistar male rats have drunk ad libitum 6% alcohol solution in water for 10 and 28 days. In both alcohol groups we have noticed significantly increase in adiponectin plasma levels and adiponectin gene expression in epididymal adipose tissue compared with control water-drinking animals (data not yet published).

On the other side, AVOGARO et al. (2003) described that moderate red wine intake does not modify the plasma concentrations of both adiponectin and TNF-α concentrations.

On the contrary, chronic alcohol consumption significantly decreased circulating concentrations of adiponectin in mice (XU et al. 2003). Reduction of adiponectin expression may be partially responsible for alcohol-induced liver injury. Since adiponectin is known to suppress TNF-α action (YOKOTA et al. 2000; OUCHI et al. 2001; STEFAN and STUMVOLL 2002), adiponectin may exert a hepatic protective effect. One possible mechanism of decreased adiponectin could be due to the elevated levels of TNF-α, which suppress adiponectin expression in adipose tissue through a paracrine or endocrine pathway. Both circulating concentrations of TNF-α and a local production of TNF-α in adipose tissue are increased at the early stage of alcoholic liver injury (LIN et al. 1998). Another possible mechanism of alcohol-induced decrease of adiponectin expression is that alcohol may act directly on adipocytes and suppress its expression (XU et al. 2003). Moreover, chronic alcohol consumption in rats has been shown to increase relative expression of stimulatory β subunit of heterotrimeric guanosine triphosphate binding protein (Gβ) in adipocyte membranes and to induce activation of the protein kinase A (PKA) pathway (WILKES et al. 1996). PKA activation can dramatically decrease adiponectin expression in vivo as well as in vitro (FASSHAUER et al. 2001; DELPORTE et al. 2002).

Therefore, the effect of alcohol on adiponectin physiology appears to depend on the amount of alcohol consumed, the diatery context, and nutritional status (YOU et al. 2005).

Resistin. CHEN and NYOMBA (2003) have found elevated resistin mRNA and protein in rats after prenatal EtOH exposure. They have shown increased resistin expression in hypoinsulinemic newborn rats exposed to EtOH during pregnancy, suggesting that hyperinsulinemia is an unlikely factor in the increased resistin expression in EtOH offspring (CHEN and NYOMBA 2001). Elevated serum glucose concentrations in these pups may have contributed to an increase in resistin expression at this early age (KIM et al. 2001, SHOIMA et al. 2002). This theory seems not to be relevant to persistently elevated resistin levels during adulthood.

Adiponutrin. Up to now there are no studies about the effect of alcohol intake on adiponutrin expression. However, it is known that alcohol increases the membrane lipid fluidity (SAUERHEBER et al. 1982). Thus, because of adiponutrin transmembrane localization, we can
hypothesize that alcohol consumption may influence apart from the expression of adiponutrin mRNA also anchoring the protein transmembrane sequence. In this way alcohol intake may affect overall stabilization of adiponutrin in adipocytes membrane and its function.

**Conclusion.** White adipose tissue is know recognized as important endocrine organ and due to its mass, such tissue appeared the largest endocrine organ in the body. Adipokines are involved in many biological and metabolic events and impairment of their gene expression and/or plasma levels may be responsible for various effects - beneficial or deleterious. Alcohol consumption, both moderate and chronic, influence adipokines levels and affects their function on target tissues this way. So far there is not enough knowledge about individual adipocytes secretory products and complex data about their consequences in the organism. Studies exploring the effect of alcohol intake on adipokines can help us to understand the pathology associated with WAT mass dysregulation.

**Acknowledgements**

This article was performed within the project of the VEGA 2/4030/4

**References**

AHIMA RS, SAPER CF, FLER JS et al.: Leptin regulation of neuroendocrine systems. Front Neuroendocrinol. 21, 263-307, 2000
BANKS WA, KASTIN AJ, HUANG W et al.: Leptin enters the brain by saturable system independent of insulin. Peptides 17, 305-311, 1996
BASKIN DG, SCHWARTZ M, SEELEY R et al.: Leptin receptor long-form splice-variant protein expression in neuron cell bodies of the brain and co-localization with neuropeptide Y mRNA in the arcuate nucleus. J. Histochem. Cytochem. 47, 353-362, 1999b
BATES SH and MYERS M: The role of leptin receptor signaling in feeding and neuroendocrine function. TRENDS Endocrinol. Metab. 14, 447-452, 2003
ALCOHOL AND ADIPOSE TISSUE HORMONES- REVIEW

CHEN L and NYOMBA LG: Prenatal alcohol exposure impairs glucose tolerance in adult rat offspring. Canadian Diabetes Association meeting, Edmonton, Canada, p 33 (Abstract 121), 2001

CHEN L and NYOMBA LG: Glucose Intolerance and Resistin Expression in Rat Offspring Exposed to Alcohol in Utero: Modulation by Postnatal High-Fat Diet. Endocrinology 144, 500-508, 2003

CHEUNG CC, CLIFTON DK, STEINER RA: Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. Endocrinology 138, 4489-4492, 1997


DE OLIVEIRA SER, FOSTER D, MCGEE HM et al.: Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. Circulation 102, 2347-2352, 2000


GAZIANO JM, BURING JE, BRESLOW JL et al.: Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N. Engl. J. Med. 329, 1829-1834, 1993


GUERRE-MILLO M: Adipose tissue and adipokines: for better or worse. Diabetes Metab. 30, 13-19, 2004


HOTAMISLIGIL GS, SHARGILL NS, SPIEGELMAN BM: Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. Science 259, 87-91, 1993


HOTTA K, FUNAHASHI T, BODKIN NL et al.: Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 50, 1126-1133, 2001


JELLINEK EM: Alcohol addiction and chronic alcoholism. New Haven: Yale University Press, 1942


JONES AW and JÖNSSON KA: Food-induced lowering of blood-alcohol profiles and increased rate of elimination immediately after a meal. J. Forensic Scienc. 39, 1084-1093, 1994


KJELDGAARD M: Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature 393, 72-76, 1998


ALCOHOL AND ADIPOSE TISSUE HORMONES—REVIEW


LOCHHEAD PA, SALT IP, WALKER KS et al.: 5-aminoimidazole-4-carboxamide riboside mimics the effects of insulin on the expression of the 2 key gluconeogenic genes PEPCK and glucose-6-phosphatase. Diabetes 49, 896-903, 2000


MAYER EJ, NEWMAN B, QUESENBERRY CP et al.: Alcohol consumption and insulin concentrations. Role of insulin in associations of alcohol intake with high-density lipoprotein cholesterol and triglycerides. Circulation 88, 2190-2197, 1993


MOORE RD and PEARSON TA: Moderate alcohol consumption and coronary artery disease. Medicine, 65, 242-267, 1986

MORASH BA, LI A, MURPHY PR et al.: Leptin gene expression in the brain and pituitary glands. Endocrinology 140, 5995-5998, 1999


OBRAĐOVIĆ T and MEADOWS GG: Chronic alcohol consumption increases plasma leptin levels and alters leptin receptors in the hypothalamus and the perigonadal fat of C57BL/6 mice. Alcohol Clin. Exp. Res. 24, 255-262, 2002


ALCOHOL AND ADIPOSE TISSUE HORMONES- REVIEW


Shapiro L and Scherer PE: The crystal structure of a complement-Iq family protein suggests an evolutionary link to tumor necrosis factor. Curr. Biol. 8, 335-338, 1998


Stasiuniene N and Praskevicius A: Peptides regulating food intake and body weight. Medicina 41, 989-1001, 2005

Stefan N, Vozarova B, Funahashi T et al.: Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 51, 1884-1888, 2002a

Stefan N, Vozarova B, Funahashi T et al.: Plasma adiponectin levels are not associated with fat oxidation in humans. Obes. Res. 10, 1016-1020, 2002b

Stefan N and Stumvoll M: Adiponectin – its role in metabolism and beyond. Horm. Metab. Res. 34, 469-467, 2002


Štrbák V, Benicky J, Macho L et al.: Four-week alcohol Intake Decreases food intake and body weight but does not affect plasma leptin, corticosterone, and insulin levels in pubertal rats. Metabolism 47, 1269-1273, 1998


Uehara Y, Shimizu H, Ohnani K et al.: Hypothalamic corticotropin-releasing hormone is a mediator of the anorexigenic effect of leptin. Diabetes 47, 890-893, 1998
VILLAFUERTE BC, FINE JB, BAI Y et al.: Expression of leptin and insulin-like growth factor-1 are highly correlated and region-specific in adipose tissue of growing rats. Obesity Res. 8, 646-656, 2000
VOGEL RA: Alcohol, Heart Disease, and Mortality: A Review. Reviews in cardiovascular medicine 1, 7-13, 2002
YOKOTA T, ORITANI K, TAKAHASHI I et al.: Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 96, 1723-1732, 2000
YOU M, CONSIDINE RV, LEONE TC et al.: Role of adiponectin in the protective action of dietary saturated fat against alcoholic fatty liver in mice. Hepatology 42, 568-572, 2005
YOUN BS, YU KY, PARK HJ et al.: Plasma resistin concentrations measured by enzyme-linked immunosorbent assay using a newly developed monoclonal antibody are elevated in individuals with type 2 diabetes mellitus. J. Clin. Endocrinol. Metab. 89, 150-156, 2004
ZLOKOVIĆ BV, JOVANOVIC S, MAJO W et al.: Differential regulation of leptin transport by the choroid plexus and blood-brain barrier and high affinity transport systems for entry into hypothalamus and across the blood-cerebrospinal fluid barrier. Endocrinology 141, 1434-1441, 2000