Adrenomedullin as A Protein with Multifunctional Behavior and Effects in Various Organs and Tissues

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Abstract

In literature, it has been reported that adrenomedullin, which is generally thought to have vasodilator, natriuretic and diuretic effects, is synthesized in almost all body, especially CNS, vascular muscles and endothelium, heart, liver, lung, kidney, gastric mocosa, intestinal endothelium and various blood cells. It has been found that the possible effects of adrenomedullin can be demonstrated directly or indirectly by means of active mediators, neuropeptides, enzymes and hormones. It is also suggested that it regulates the endocrine system by affecting the hypothalamic-pituitary axis. It increases in heart failure, acute coronary syndromes, hypertensive conditions, cerebrovascular accessory, chronic renal failure and periodontitis and decreases in peptic ulcer and intestinal diseases. However, it is still not clear whether increase/decrease in adrenomedullin level is a cause of a disease or is a result of damage due to an illness. This peptide, which could be thought to multifunctional, should be considered as a molecule with genetic coding that may have different effects on different tissues and conditions. For all these reasons, we aimed to review the multifonctional behavior of adrenomedullin in the light of the current literature to pioneer new hypotheses and discuss possible mechanisms.

Introduction

Adrenomedullin was first described by Japanese scientists in 1993. These researchers discovered a new peptide while searching for the effects of peptides on cAMP levels in rat thrombocytes. The peptide was named adrenomedullin (ADM) as it was extracted from adrenal medulla [1]. Following researches have revealed that this peptide was not only found in adrenal medulla but it was also detected in heart, vessels, kidneys, lungs, gastrointestinal tract, central nervous system (CNS) and endocrine tissues [2]. ADM was found to be present in circulation and various biological fluids and synthesized by different tissues. It is reported to function both as a generalized hormone and locally affecting autocrine or paracrine mediator [3, 4].

Altough initially thought a hypotensive and natriuretic peptide related to vascular structures, laterly it was found that adrenomedullin has various effetcs like growth, and differentiation on different tissues like renal, edndocrine, CNS and peripheral tissues [1-5]. It exerts these effects either directly or indirectly via some active mediators, neuropeptides, enzymes and hormones [4, 6-8]. Afterwards, it was found that it was elevated in heart failure, acute coronary syndrome, hipertensive situations, cerebrovascular events, chronical kidney failure, sepsis and periodontitis, while diminished in peptic ulcus and intestinal disease [1, 5, 9-15]. Besides these, adrenomedullin has drawn attention as it stimulates the proinflammatory cytokine IL-6 and supresses cytokines like TNF- α for regulating inflammation, being a potent of inhibitor of apoptosis and stimulating angiogenesis in tumor cells [16-19]. However, there is still a lot of information gap on adrenomedullin. Unfortunately, evidences explaining these multifunctional effects of adrenomedullin have not yet reached. Therefore, there is a need for new hypotheses to discuss possible mechanisms that may explain these effects.

Structure and Synthesis

Adrenomedullin gene is located on chromosome 11 and contains 3 intron and 4 exon domains. Transcriptionally activated TATA, CAAT, GC boxes and, nuclear factor-interleukin 6 (NF-IL-6) and activator protein-2 (AP-2) domains are found at the 5' end of this gene. The AP-2 region activates the protein kinase C (PKC)-cAMP cascade [20], whereas the NF-IL-6 region is the site where acute phase proteins, which are particularly effective in inflammation, bind. The binding of many cytokines involved in the inflammation to the NF-IL-6 region stimulates human ADM synthesis of 52 amino acids and subsequently accelerates blood flow in the area of inflammation [1, 21].

ADM is included in calcitonin/CGRP/amylin family as it has a slight resemblance in sequence to calcitonin gene-related peptide (CGRP) [1]. mRNA responsible for ADM synthesis encodes information for the synthesis of a preprohormone known as preproadrenomedullin with 185-amino acid. Later, 21 amino acid signal peptide is cleaved from preproadrenomedullin [1-185] and the 164 amino acid peptide proadrenomedullin (proADM) [22-185] is formed [22, 23]. Proadrenomedullin has three vasoactive peptides: ADM, proadrenomedullin N-terminal 20 peptide (PAMP) and adrenotensin. In addition, it has an inactive domain known as MR-proADM. Afterwards PAMP [22-41], mid-regional proadrenomedullin (MR-proADM) [45-92], ADM [95-146] and adrenotensin [153-185] are detached from proADM. ADM, detached from proADM precursor, is an immature and inactive molecule of 53 amino acids bound to glycine called "ADM-glycine". Glycine is then removed by amidation and 52 amino acid active form is obtained. This active form is called "ADM-mature" [24, 25] (Figure 1).

Production and Metabolism

Tissues with highest ADM mRNA levels are reported to be adrenal medulla, heart, lungs and kidneys [22]. Besides these, it was found to be synthesized in gastrointestinal, endocrine and central nervous system, reproductive system cells, vascular smooth muscle and endothelial cells [26]. It has also been detected in body fluids like blood, urine, saliva, cerebrospinal fluid, sweat, amniotic fluid and breast milk [3, 4, 26]. As it is found in almost all tissues and body fluids, it brought out the thought that ADM has multiple biological functions. That is why there are many ongoing studies about ADM currently.

Production and metabolism of ADM is very fast with a half-life of 20 minutes [27]. It is carried in circulation with a specific protein called adrenomedullin binding protein-1 (AMBP-1) [28]. Another interesting
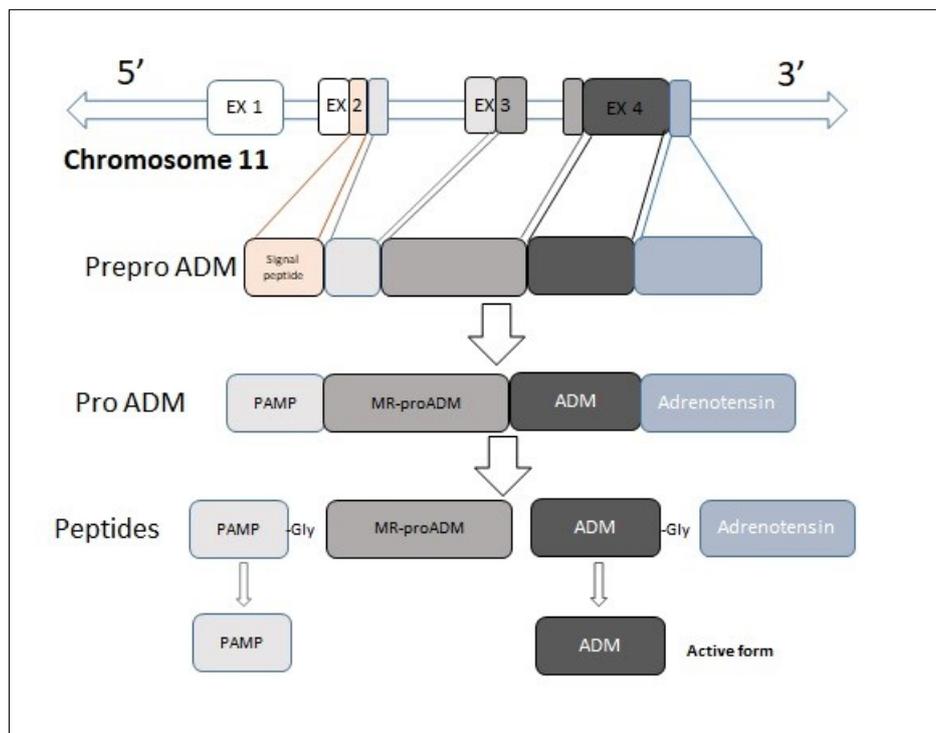
Figure 1. Biosynthesis ADM. Adrenomedullin is inactive form when glycine is bound.

feature of ADM is that it does not have circadian rhythm and plasma levels are not affected by age and gender [29]. Plasma ADM levels also were found to be not affected by food or water intake and to be stable all day [30].

Although it is defended that ADM is not stored and secreted continuously [31, 32], there are several studies known to report that ADM is stored in tissues of the pancreas and adrenal medulla [33]. The major form of ADM in circulation is immature or inactive ADM-glycine form [25]. Metalloproteinases and aminopeptidases are shown to be effective in ADM catabolism [34].

ADM synthesis and release are under the control of many factors. Particularly cytokines (such as IL-1α, IL-1β, TNF-α and TNF-β), liposaccharides [35] and endotoxins [36] strongly stimulate the synthesis of ADM. This, in turn shows that ADM has a strong relationship with inflammation and sepsis. Steroids hormones like glucocorticoids, peptide hormones like thyroxine [37], mediators like AT II [38], endotelin-1 [39] and bradykinin [40], atrial natriuretic peptide (ANP) [41] and arginine vasopressin (AVP) [42] stimulate ADM

synthesis. Besides these, higher altitudes, hypoxia [43] and pregnancy [44] are known to elevate plasma ADM levels.

ADM Receptors and Signal Pathways

ADM is a member of calcitonin peptide family, which also includes calcitonin, calcitonin-gene related peptide (CGRP) and amylin [1]. Its functions in the body are mediated by CGRP and adrenomedullin receptors. These receptors are receptors, which are called calcitonin receptor-like receptor (CLR), which are seven transmembrane folding and a kind of G protein [45]. In order for CLR proteins to function, they need proteins (RAMPs) with three types that alter receptor activity. CLR/RAMP1 complex serves as CGRP receptor, while CLR/RAMP2 complex serves as ADM1 receptor and CLR/RAMP3 complex serves as ADM2 receptor [46, 47, 48] (Figure 2).

ADM performs its effect mostly by activation of protein kinase A (PKA) by increasing intracellular cAMP levels [49]. ADM also increases intracellular Ca^{++} independent from cAMP and activates endothelial NO synthase (eNOS) which induces NO release and causes vasodilatation [50]. It has also been shown to induce NO
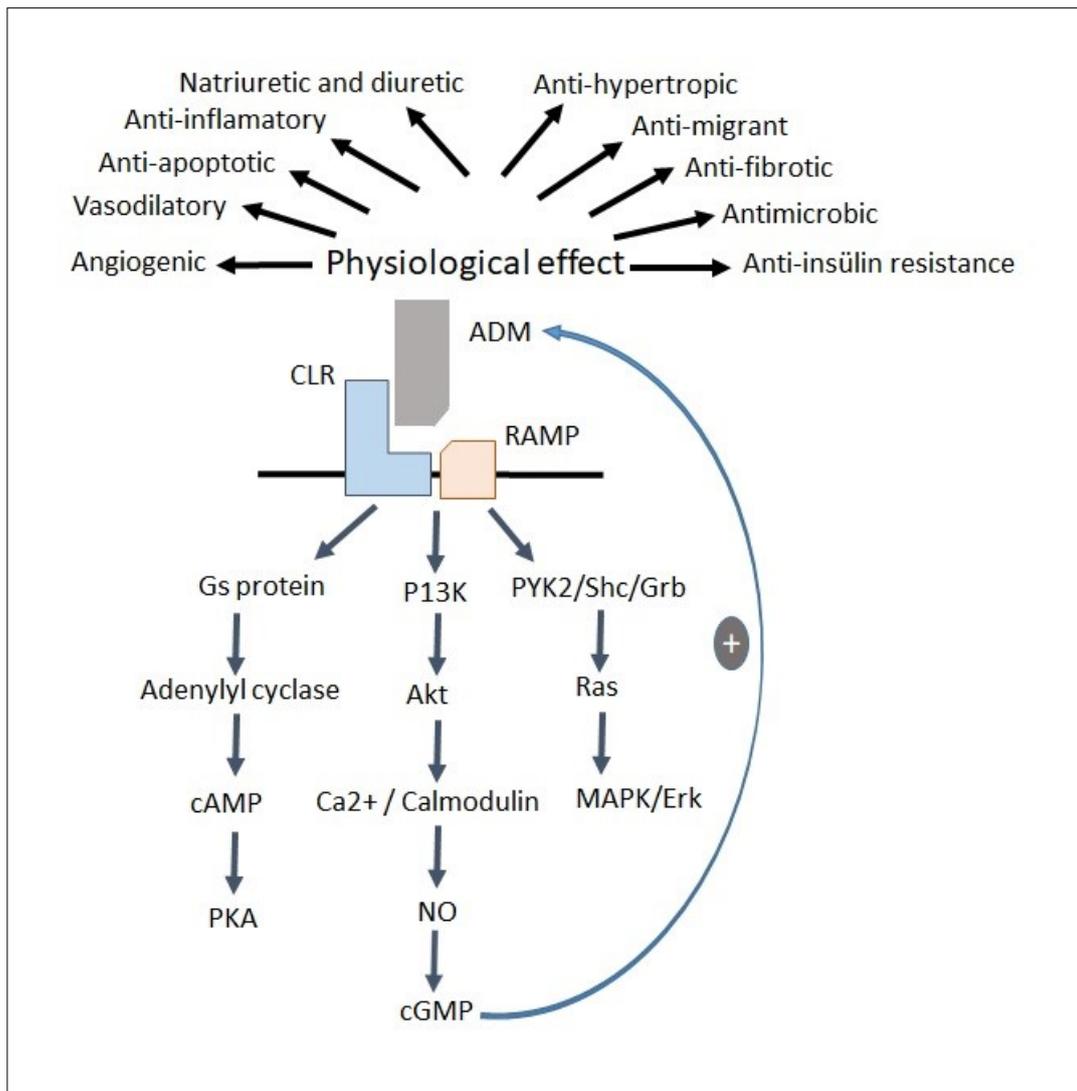
Figure 2. Signal pathways and effects of adrenomedullin.

synthesis by inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells [51]. Vasodilatory effect of ADM is known to be caused by NO release [52]. ADM also increases NO-activated guanosine 3', 5'- cyclic monophosphate (cGMP) levels and causes protein kinase G (PKG) activation (NO/cGMP/PKG signal pathway) [53]. Besides these pathways, it also uses different signal pathways like mitogen-activated protein kinase (MAPK) [54], K^+-ATP channel activation [55], c-fos expression [56] and phosphatidyl-inositol-3-kinase/akt dependent pathway [57].

ADM Measurement

Reliability of ADM measurement is limited by factors like the molecule being unstable [30], having a short half-life [27] and binding to a specific protein in circulation. MR-proADM generated from prepro ADM is an inactive form, it is more stable and has a longer half-life when compared to ADM. ADM and MR-proADM are produced in equal amounts by posttranslational processes [30]. Plasma MR-proADM concentrations are also known to reflect ADM concentrations directly and MR-proADM measurement has some advantages. One of these advantages is that the MR-proADM measurement has a higher diagnostic accuracy [30, 58].

In studies carried out in healthy individuals, plasma ADM reference values were detected with radioimmunoassay (RIA) method ranging from 2.1 ± 0.7 pmol/L to 3.3 ± 0.39 pmol/L [59, 60]. Comparison of different immunoassay methods revealed plasma ADM reference interval to be between 1-10 pmol/L [4]. Hence, plasma MR-proADM mean value measured with immunoluminometric method in

healthy individuals was reported as 0.33 ± 0.07 nmol/L [30]. These values are 1000 times higher than mature ADM levels for which given reference interval is 2.7-10.1 pmol/L [30]. That is why it became more possible to detect MR-proADM levels more in a more sensitive and accurate way.

Cardiovascular Effects

Adrenomedullin is synthesized and released in vascular smooth muscle cells [61] and endothelial cells [62]. With its strong vasodilator feature, it reduces both systemic and peripheral vascular resistance. Thus, they decreases blood pressure for longer periods and increases blood flow [63]. The vasodilatation effect of ADM can be expressed by activating the protein kinase-A cAMP (cAMP/PKA) [64] and NO/cGMP cascade [52] and ATP-sensitive potassium (K-ATP) channels [65]. The effect of ADM on vascular smooth muscle cells was found to be bidirectional. It inhibits cell proliferation and migration in medium induced by platelet-derived growth factor (PDGF), but stimulates cell proliferation in medium not induced by PDGF [66].

Plasma ADM concentrations have been observed to increase as arterial stiffness and atherosclerosis increases, which is one of the most important cardiovascular risk factors and can be evaluated by indirect pulse wave velocity [67]. Similarly, patients with chronic ischemic stroke, ADM levels were found to be increased in relation to the severity of atherosclerosis in the carotid artery [68]. It has been found that ADM has a protective effect against atherosclerosis by anti-apoptotic feature in endothelial cells and anti-proliferative and antimigrate feature in vascular smooth muscle cells [66]. In this protection, the anti-inflammatory effect of ADM was considered quite large. It has also been reported to provide the regeneration of the damaged endothelial layer by stimulating angiogenesis [69]. In addition, ADM prevents cardiovascular damage by decreasing oxidative stress [70].

ADM was found to be increased in arterial hypertension and even correlated with the degree of hypertension [71]. This elevation in ADM is thought to provide a compensatory mechanism by vasodilator, natriuretic and diuretic action [72]. ADM was also found to increase cardiac output and heart rate [73, 74].

In the studies, ADM showed a (+) inotropic effect with a Ca^{++} and CGRP receptor- dependent pathway in the rat heart and (-) inotropic effect with a NO-dependent pathway in the rabbit heart [75,76,77]. However, different results have been obtained about the effect on the contractility of the human heart. In one study, it was found that ADM in human myocardyocytes had an inotropic effect by inhibiting β-adrenergic stimulation [78]. It has been also reported that cAMP/PKA pathway is stimulated in human atrium (compared to ventricles) and has (+) inotropic effect [79]. ADM inhibits cardiac hypertrophy by activating cAMP/PKA [80]. All these contradictory results show that there is no consensus on the cardiac effects of ADM.

Nishikimi et al. found that ADM levels in heart failure increases as correlating intensity of disease and ADM increases when left ventricular ejection fraction decreases [81]. It has been suggested that ADM may be a prognostic indicator in ischemic left ventricular dysfunction [82]. Since inflammation is important in the pathophysiology of heart failure [83] and ADM is a strong response to endogenous cytokines in inflammation, it has been suggested that ADM may be useful in determining the prognosis of heart failure [84]. According to a recent study, high ADM levels at an early stage of myocardial infarction [85] confirms this prognostic significance. Nakamura et al. showed that ADM increases coronary blood flow by coronary vasodilatation. It is also stated that ADM restricts affected ischemic area by preventing apoptosis of myocytes, oxidative stress and providing cardiac remodeling [86]. This information should be considered as evidence that the detection of ADM levels may be critical in the prognostic of coronary heart disease.

Renal Effects

ADM is synthesized by both glomerular and tubular cells in the kidney. The fact that the amount of adrenomedullin detected in urine is higher than that of blood suggests that kidneys may have a role in the clearance of ADM [59]. It has been reported that ADM has a diuretic and natriuretic effect by increasing renal blood flow and glomerular filtration by means of vasodilatation resembling ANP and BNP with a NO-dependent mechanism in arterioles [72, 87]. In

summary, the peptide shows diuretic and natriuretic effect by increasing glomerular filtration and reducing tubular sodium reabsorption.

ADM has an important role in the mesangial cell physiology. ADM induced by proinflammatory cytokines such as IL-1β and TNF-α in mesangial cells shows antioxidant effect by decreasing both anti-inflammatory and free radical formation. ADM activates cAMP/PKA signaling pathway and decreases the generation of reactive oxygen metabolites in mesangial cells dose-dependent, and inhibits cell proliferation. It also suppresses mitogenesis by the MAPK-dependent route in vascular smooth muscle cells and mesangial cells. These effects show that ADM provides both immune and inflammatory protection by suppressing glomerular damage [88]. The high level of ADM levels in patients with chronic glomerulonephritis also support this consensus [89].

ADM also plays an important role in the endocrine function of the kidney. However, there are various ideas about that effect on the renin-angiotensin-aldosterone system. ADM reduces arterial pressure while increasing cardiac output by functional antagonist action of angiotensin II in vascular and zona glomerulosa of adrenal gland. The attenuation of angiotensin-inducible aldosterone synthesis while increasing plasma renin activity is thought as evidence that ADM partially interacted with the renin-angiotensin-aldosterone system [90]. In rats, there are studies that increase the renin release secondary to the hypotensive effect of ADM [91], but continuously reduces the renin activity of ADM administered externally [92]. It was also suggested that plasma ADM levels were elevated in chronic renal failure [93] and correlated with plasma creatinine levels [71]. In general, ADM has been widely investigated in the field of nephrology because it has vasodilator and hypotensive effect, antiproliferative effect in mesangial cells and two-way effect on renin release.

Pulmonary Effects

It has been suggested that lungs are the main tissue where ADM is cleansed from the body [26]. It is claimed that ADM acts as a vasodilator and bronchodilator in the lungs and inhibits acetylcholine and histamine-induced bronchoconstriction [94]. In

particular, it has been reported that blood ADM levels increase in acute asthma exacerbations, and this has a bronchodilator effect [95]. Pulmonary vasodilatation due to ADM in hypoxia has been reported to occur via prostaglandins rather than NO [94]. In patients with pulmonary hypertension, blood ADM levels were found to be increased as protective mechanism [96]. In another study conducted in rats with heart failure with pulmonary hypertension, ADM was found to decrease the right ventricular systolic pressure [10]. ADM has also been reported to contribute to the anti-inflammatory process by dose-dependent inhibition of cytokine-induced neutrophil chemoattractant (CIMC) release from lipopolysaccharide-induced alveolar macrophages [97].

Effects of Central Nervous System

ADM receptors have been widely distributed throughout the central nervous system. ADM receptors have been detected in many areas such as cerebral cortex, cerebellum, pons, medulla oblongata, thalamus and hypothalamus [98]. The fact that ADM levels in the cerebrospinal fluid are lower than the plasma levels indicate that the secretion of ADM from the cerebrospinal fluid occurs independently of plasma [44]. It has been reported that ADM increases the blood flow by vasodilatation in the cerebral circulation and increases the production of cAMP/PKA pathway and NO in the vascular smooth muscle cell, especially in large-scale cerebral vessels, causing vasodilatation [64, 52].

In the case of hypoxic ischemia and hypoglycemia, it has been observed that ADM gene expression is increased in central cortex neurons, endothelium and perivascular glial cells [99]. Cortisol, NO and ADM levels were higher in chronic schizophrenia than control group [100]. Increased ADM mRNA expression was detected in ischemic cortex in rats with stroke formed by occlusion of the middle cerebral artery [101]. ADM infusion after hypertrophic rupture of the middle cerebral artery has been shown to increase regional blood flow and collateral circulation, thus reducing ischemic brain damage [102]. As a result, it is understood that ADM has important effects in post-ischemia reperfusion.

Effects on Hypothalamic–Pituitary–Adrenal Axis

ADM has been shown to inhibit ACTH secretion from rat anterior pituitary cells in a dose-dependent manner, reducing CRH-induced ACTH production and performing all of these with a mechanism independent of cAMP [103]. ADM levels were found to be quite high and significantly decreased after surgical treatment in patients with Cushing's disease due to pituitary adenoma [104].

ADM has been reported to inhibit the salt appetite in rats by controlling oxytocin (OT) release in the hypothalamus. ADM has been shown to change water intake, salt appetite and food intake when given directly to the brain. It has also been reported that central ADM stimulates OT release by affecting CNS and inhibits more Na consumption [105, 106]. The effect of ADM via a neurotransmitter OT suggests that many processes related to OT can be regulated via ADM. It was found that OT stimulates uterine muscle contraction, facilitates delivery and helps protect the brain from hypoxia, regulates the menstrual cycle and ejaculation of men, decreases the repetitive behaviors in diseases such as autism, prevents the proliferation of breast cancer and other tumor cells, stimulates angiogenesis while reducing inflammation, provides cardiac repair in ischemia-reperfusion injury and it also has apoptosis-inhibitory effects in the heart [107-112]. We believe that at least some of these effects of OT may be under the influence of ADM.

CNS-induced ADM is considered as a physiological regulator of thirst. It is suggested that brain-derived ADM increases vasopressin secretion and therefore acts as a physiological regulator of fluid homeostasis [113]. ADM is synthesized and released in both adrenal cortex and adrenal medulla. ADM and its receptors have been found to be intense in the adrenal cortex, especially in the area of the zona glomerulose [114]. ADM has been shown to inhibit aldosterone production but has no effect on plasma renin activity and plasma corticosterone (or K^+) levels [115]. However, in another study, an increase in plasma renin activity was observed after ADM infusion to sheeps and cortisol decreased. This study also showed a decrease in ACTH levels. The decrease in cortisol levels was thought to be due to a decrease in ACTH, not a direct effect on the adrenal cortex [116]. In addition, it

was observed that synthetic ADM application increased the adrenal blood flow in rats and this has led to the use of ADM for therapeutic purposes [117].

Reproductive Effects

ADM is found in the myometrium and endometrium layer of the ovary and uterus of women [118, 119]. ADM levels were high in the follicular phase of the menstrual cycle and low in the luteal phase [120]. It has been suggested that ADM produced by granulosa cells may play a role in the development of corpus luteum [121]. ADM has been found to play an important role in the growth of placenta and fetus and prevention of uterine contraction by providing blood flow to uterus (blood supply to the placenta) and implantation of the embryo [122-126]. ADM is thought to be present in the blood, placenta and amniotic fluid during normal pregnancy due to the important tasks it undertakes in all these stages [44, 127].

ADM was detected in testis, epididymis and prostate in male genital tract [128-130]. The expression of ADM gene is shown in the sertoli and leydig cells in the testis [131-132]. It has been suggested that ADM affects sperm maturation and movement, inhibits contraction in prostate and stimulates prostatic blood flow [128, 133-135]. ADM has also been reported to cause vasodilatation via NO/cGMP in cavernous vascular endothelial cells [57].

Effects on Immune System and Inflammation

ADM has complex effects on inflammation. It has been reported that plasma ADM levels are increased in the local and systemic inflammation and are synthesized in mucosal surfaces and contributes to anti-microbial protection [136]. It controls the leukocyte migration and differentiation, while increasing the blood flow in the inflammation zone. It also reduces endothelial permeability and inhibits exudate formation [137]. In addition, the fact that it may have local effects suggest that it can be used with topical drugs. Therefore, we consider that it can be used in the treatment of edema.

ADM has been found to play a regulatory and stabilizer role among proinflammatory and anti-inflammatory cytokines. Proinflammatory markers, TNF-α and IL-1β, have been seen as potent stimulators of ADM release [138, 22]. ADM also stimulates

proinflammatory cytokine release, such as IL-6 and IL-10 while IL-10 also shows anti-inflammatory effect by suppressing TNF-α and IL-1β release [16, 139]. ADM is transported in the plasma by binding to the complement factor H, known as adrenomedullin binding protein-1 (AMBP-1). In this way, ADM plays an active role in the regulation of the complement system. It also increases the cleavage of C3b through factor I and it affects the complement regulator function of factor H [28]. Since ADM levels were significantly elevated in sepsis and septic shock (especially in endotoxic shock), ADM was thought to be secreted as a preservative against sepsis [140, 141]. As a result, ADM regulates the immune system by functioning through both cellular and secretory (cytokines and complement) system. We think that ADM has significant potential as an agent that can be used in the treatment of septic shock due to its anti-inflammatory effects.

Gastro-Intestinal Effects

Immunoreactive ADM has been detected in various tissues including plasma, as well as kidney, pancreas and intestine [142]. It is reported that ADM may act as autocrine or paracrine way in these tissues where it is released as a vasoactive hormone in the circulation [71, 143]. Subcutaneous ADM was found to have anti-ulcer effect in rats with reserpine-induced gastric mucosal damage. Probable cause of this effect is possibly associated with accelerative effect of ADM on blood flow in the gastric mucosa and partially anti-gastric secretory activity by increasing the release of NO [144]. Rossowski et al. previously reported that ADM strongly inhibits gastric acid secretion [145]. All these findings suggest that ADM may be an anti-ulcer agent.

ADM and PAMP are able to regulate many physiological and pathological conditions such as intestinal hormones. It has also been reported that it has a regulatory role in small intestine and colon peristaltism. It is also argued that ADM and PAMP regulate the intestinal mucosa and help the mucosal host defense system. In addition, it is also thought that ADM and PAMP deficiency may be effective in the development and progression of intestinal diseases with its effect on microbiota composition [146]. However, the use of ADM as an antimicrobial agent requires more investigations that are precise.

Relationship Between Adrenomedullin, Thyroid Hormones and Obesity

In a study investigating the effect of thyroid hormones on ADM, ADM levels were higher in hyperthyroid rats and lower in hypothyroid rats compared to control group [8]. Higher ADM and PAMP levels with higher thyroid hormones were detected in cultured vascular smooth muscle cells (VSMC) and thyroid storm due to Graves' disease [147, 37, 148, 149]. Therefore, thyroid hormones are thought to regulate the production of ADM in vivo.

Due to significant effects on oxygen consumption and metabolic rate, thyroid hormones are essential for normal operation of almost all tissues. For this reason, the relationship between thyroid hormones and ADM is also a matter of curiosity. It has been reported that thyroid hormones increase the oxygen capacity of blood by increasing erythropoietin (EPO) production and increase tissue perfusion by vasodilation via accelerating ADM synthesis [150, 37]. In addition, it was stated that direct ADM synthesis could be stimulated via thyroid hormones in case of hypoxia [151]. Therefore, it is considered that important part of ADM's effect on energy metabolism is carried out by thyroid hormones.

Fat-rich diet increases ADM secretion [152], ADM stimulates lipolysis in brown adipose tissue [153] and adipose tissue adipocyte differentiation [154]. Due to these effects, it is important to use it in combating obesity.

There are views that ADM is stored in pancreas secretory granules. ADM has been shown to inhibit insulin secretion by inhibiting β cells in the pancreas [33]. It was also emphasized that high ADM levels in DM patients may be caused by hyperglycemia-induced ADM expression [155]. On the other hand, it has been suggested that ADM levels are not affected by plasma glucose concentrations [156]. Circulating ADM concentrations have been reported to be higher in pregnant women with gestational DM, and have been reported to suppress insulin secretion in pancreatic β-cells in vitro [157].

Obesity, resulting from the expansion of adipose tissues, is characterized by impaired insulin sensitivity of target organs and triggers type 2 diabetes, and also closely related to the proinflammatory (due to its effect on TNF-α) and immune systems [158, 159, 160, 161]. We think that the relationship between ADM and proinflammatory and inflammatory regulation is the key mechanism in the relationship between obesity and ADM. However, the role of adaptive immune response in the inflammation of adipose tissue remains unclear.

In a study aiming to indicate the role of adipose tissue inflammation on the pathogenesis of insulin resistance (IR), a short-term high-fat diet was found to increase the number of CD4 (+) T cells in adipose tissues. This increase in the number of CD4 (+) T cells may contribute to the local inflammatory response in the early inflammation phase of adipose tissue and this may have an important role in insulin resistance. Major histocompatibility complex class II (MHCII) dependent antigen presentation for activation of CD4 (+) T cells has been suggested to induce early inflammation and IR in adipose tissue. MHCII inhibition is reported to decrease IR [162, 163].

In a study with transgenic mice, ADM 2 treatment was determined to fix the high fat diet induced early insulin resistance in the fat tissue. It is assumed that this is mainly achieved by inhibiting adipocyte MHCII-dependent antigen presentation and CD4 (+) T-cell activation [163]. This finding has been found to be of interest as featured as a peptide with anti-insulin resistance effect.

In a study investigating ADM regulation in obesity and its localization in human adipose tissue, it is considered as a new member of the adipokine family due to being produced from stromal cells of human adipose tissue, including macrophages and synthesized in individuals with metabolic syndrome, especially in the omental region [161].

All of these indicate that ADM may have an important role in energy use and metabolism and obesity-induced insulin resistance as well as its relationship with thyroid hormones. However, since this issue needs clear evidence, there are many things to be investigated.

Conclusion

ADM has Multifunctional Behavior as Outlined Below;

a) have significant potential as an agent for the treatment of septic shock due to its anti-inflammatory effects, b) have a possibility of taking an active role in the breakdown of insulin resistance in obesity, c) may accelerate tissue perfusion by means of thyroid hormones, d) play a regulatory and stabilizing role among proinflammatory and anti-inflammatory cytokines, e) possibly contribute to the implantation of the embryo by providing the blood supply to the uterus and placenta, f) may have bronchodilator activity especially in acute asthma attacks, g) exhibits diuretic and natriuretic effect by increasing renal blood flow and glomerular filtration by vasodilatation with a NO-dependent mechanism in the arterioles, h) effect on plasma renin activity, i) have significant effects in post-ischemia reperfusion at CNS, j) alters thirst, salt appetite and food intake by stimulating OT synthesis k) lowering blood pressure while increasing blood flow, l) protects against atherosclerosis by having anti-apoptotic effect on endothelial cells and anti-proliferative/ anti-migrate effects on vascular smooth muscle cells in ischemic heart disease m) contributes to intestinal mucosal microbiota and provides antimicrobial host defense system, and finally n) stimulates angiogenesis and regenerates the damaged endothelial layer. This multifunctional feature of ADM brings it into the forefront for the purpose of treatment and leads to perform increasing amount of researches in recent years.

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