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## VASCULAR DYSFUNCTION AND PERIADVENTITIAL ADIPOSE TISSUE

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**Summary.** Over the last years, concerted efforts have helped to uncover and understand the basic mechanisms of periadventitial regulation of arterial tone by perivascular adipose tissue. Basically, perivascular adipose tissue serves as source for “Adipocyte-derived relaxing factor” (ADRF), an essential player in the control of vascular tone of visceral and other arteries. Importantly, its disturbed local, paracrine activity is able to cause vascular dysfunction. Hydrogen sulfide (H<sub>2</sub>S) is a putative candidate for ADRF, which has received increased attention. The importance of this and other candidates for periadventitial vasoregulation has been recently explored in rodent models of obesity, hypertension and metabolic syndrome. Pharmacological tools have been successfully used to clarify the role of potassium channels involved in these conditions. Vasoactive factors of adipocytes or their receptors could represent targets for the development of novel cardiovascular drugs.

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Obesity in the last few decades has rapidly developed into a major health problem affecting a large portion of the world population. Cardiovascular disease remains the leading cause of death worldwide fueled by arterial hypertension and diabetes mellitus. These two risk factors are driven by the occurrence of obesity, which increases in all countries of the world. In North America, the population of people with overweight (body mass index, BMI>25 kg/m<sup>2</sup>) or obesity (BMI>30 kg/m<sup>2</sup>) exceeds the population with normal weight and underweight, with the latter now constituting a minority in the population. There is no reason to believe that Europeans, Asians, South Americans, Africans and other populations are spared from this trend (<http://www.who.int/mediacentre/factsheets/fs317/en/>). In Germany, about 70 % of men and 50 % of women are overweight or obese [22]. The consequences are staggering, especially as life expectancy in the United States of America is expected to shorten due to obesity [25].

#### Obesity hypertension

Obesity hypertension is the most common form of secondary hypertension. The Framingham study has already demonstrated a strong correlation between obesity and hypertension [29]. The incidence of hypertension in extremely obese individuals (BMI>35 kg/m<sup>2</sup>) is increased by a factor of three compared to non-obese individuals. Results of the

Framingham study show that an increased BMI is an independent risk factor for death from heart failure [14]. In fact, obesity is solely responsible for 11 percent of cases in men and 14 percent of cases in women of death from heart failure. These and more recent epidemiological data demonstrate the close relationship between obesity and cardiovascular morbidity and mortality [1]. Overweight as a cardiovascular risk factor is therefore a focal point of the current research. The exact relationship between visceral obesity and increased cardiovascular morbidity, in particular the underlying mechanisms, however, are largely unknown.

Adipose tissue is an endocrine organ that secretes a variety of biologically active molecules into the circulation. These molecules include adiponectin, vascular endothelial growth factor, tumor necrosis factor- $\alpha$ , interleukin-6, leptin, resistin, insulin-like growth factor and sex hormones [3, 5]. However, in addition to its function as a source of classical endocrine hormones, adipose tissue can also act as an important paracrine regulator of cells and organs. In fact, almost all arteries of our body are enveloped by perivascular adipose tissue. An increasing number of research groups have begun to study possible paracrine functions of adipose tissue in cardiovascular health and disease.

#### Adipocyte-derived relaxing factor

In 2002, our research group made the fundamental observation that visceral perivascular adipose tissue can directly regulate vascular tone of aortic rings and mesenteric arteries of Sprague-Dawley rats without involvement of the sympathetic nervous system. This new principle of paracrine regulation of vascular tone is based on the release of an “adipocyte-derived relaxing factor” (ADRF), which relaxes the smooth muscle cells by opening K<sup>+</sup> channels [19]. Several other research groups have subsequently confirmed this conceptual finding in various arteries of different species, including in humans [8, 13, 21]. A hallmark of this regulatory pathway resides in the mediation of the vasodilatory effects of ADRF by opening of voltage-gated (K<sub>v</sub>) potassium channels in the vascular smooth muscle cells (ADRF-K<sub>v</sub> signaling pathway), which can be blocked by 4-aminopyridine [27].

The chemical identity of ADRF is not yet known and is different from other – previously known – adipokines with vasoactive effects, such as tumor necrosis factor- $\alpha$  and leptin [10]. Additionally, we have demonstrated that adiponectin exhibits ADRF features, but does not act as a paracrine regulator of vascular tone by opening of K<sub>v</sub> channels [4].

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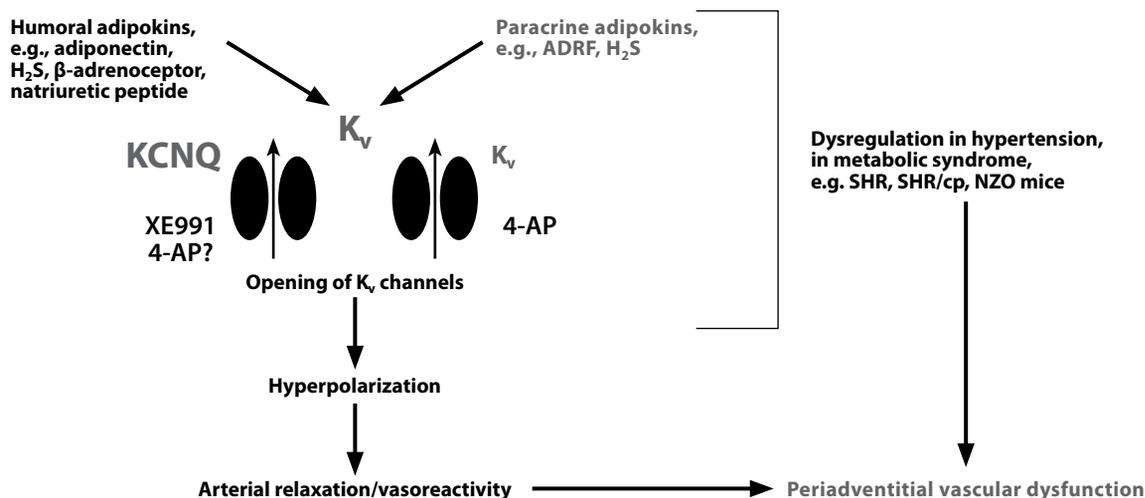


Figure 1. Vasoregulation by humoral and paracrine adipokines.

Adipose tissue is able to release humoral adipokines into the circulation to produce arterial relaxation by opening voltage-dependent ( $K_v$ )  $K^+$  channels in the plasma membrane of smooth muscle cells. ADRF is released by perivascular adipocytes in response to vasoconstrictors (such as serotonin) and primarily produces endothelium-independent arterial relaxation by opening smooth muscle cell  $K_v$  channels. At least in part, KCNQ ( $K_{v7}$ ) channels could represent the subtype of  $K_v$  channels involved. Native KCNQ channels are blocked by XE991 and possibly by 4-aminopyridine (4-AP). It is possible that additional subtypes of  $K_v$  channels play a role in the effects of ADRF, which are sensitive to 4-AP. H<sub>2</sub>S could represent ADRF, at least in rats. This signaling pathway is mal-functional in a number of polygenetic rodent models of hypertension, such as spontaneously hypertensive rats (SHR), corpulent SHR/cp rats and New Zealand obese (NZO) mice.

A number of research groups became involved in search for the chemical identity of ADRF. Bob Lee's group focused mainly on Ang (1–7) signaling. This group has proposed that Ang (1–7) is released from perivascular adipocytes and leads to relaxation via activation of MAS receptors [17]. The group led by Tony Heagerty is largely focused on adiponectin [20, 28]. Interestingly the effects of both factors are presumed to involve opening of Ca<sup>2+</sup>-activated maxi potassium channels and are largely dependent on the endothelium, thus it is rather unlikely that these “perivascular relaxing factors” represent ADRF(s) [4]. It is surprising that the anti-contractile effect of perivascular adipose tissue lost in obesity can be rescued using melatonin; though, rescue by adiponectin has not been studied by this group [2]. The group of Tony Lee proposed methyl palmitate as perivascular adipose tissue-derived relaxing factor in the rat aorta [18]. Similarly to ADRF, 4-aminopyridine inhibits the relaxant effects of this factor; therefore methyl palmitate exhibits indeed ADRF-like properties [18] and could represent a potential ADRF.

We investigated whether ADRF is a gaseous mediator. We were able to rule out that carbon monoxide is ADRF. However, coinciding with a Chinese research group, we obtained data suggesting that the “third gas” H<sub>2</sub>S may represent ADRF. Consistent with this view, we found that inhibitors of the H<sub>2</sub>S-producing enzyme cystathionine gamma-lyase inhibit the effects of ADRF in the rat aorta. Moreover, exogenous H<sub>2</sub>S can mimic ADRF effects [24]. Nevertheless, our recent work indicates that additional factors can act as ADRF, at least in the mouse [15, 16].

#### Potassium channels

On the search for the chemical nature of ADRF, we succeeded in identifying putative  $K_v$  potassium channel(s) involved in ADRF signaling: among the 12 families of  $K_v$  channels

( $K_{v1}$ – $K_{v12}$ ),  $K_{v7}$  channels, also called KCNQ channels, seem to act as target structures of ADRF (and possibly H<sub>2</sub>S [24]). KCNQ channels (KCNQ 1, 3, 4, 5) have only recently been identified in vascular smooth muscle cells and were initially thought to be functionally insignificant because they are inactive at resting conditions and are not involved in the myogenic arterial response [23]. Our recent observations indicate, however, that ADRF seems to represent the physiological activator of KCNQ channels in vascular smooth muscle cells [11, 12, 26]. Notably, we observed an attenuated paracrine (ADRF) effect of visceral perivascular adipose tissue on mesenteric arterial tone in spontaneously hypertensive rats and New Zealand obese mice [4, 6, 7]. We also showed that the disturbed ADRF- $K_v$ -signaling can be “normalized” in peripheral resistance arteries by synthetic KCNQ channel openers in spontaneously hypertensive rats and New Zealand obese mice [30]. Interestingly, “normalization” of the ADRF effect was accompanied by a reduction of systemic blood pressure, suggesting that ADRF- $K_v$  could be necessary for the regulation of blood pressure. However, the KCNQ subtype(s) involved is still unclear and needs to be defined in future studies (Fig. 1).

#### KCNQ and novel drugs

Our attempts using *Kcnq1*<sup>-/-</sup> mice have suggested that KCNQ1 are unlikely involved in ADRF effects. We therefore speculate that KCNQ3, KCNQ4 and/or KCNQ5 channels may play an important role (Tsvetkov et al., 2015, submitted). A better understanding of the role of these periadventitial stress signals could thus be a new starting point to explain the increased cardiovascular risk and the increased prevalence of hypertension in visceral obesity and metabolic syndrome and to develop novel therapeutic approaches. We have hypothesized that these approaches need to consider that perivascular adipose tissue is not

homogenous, but non-uniform. This obvious regional heterogeneity and diversity of perivascular adipose tissue has the consequence that it may exhibit different paracrine effects on the vascular structure and function, with immediate consequences for particular disease states, such as endothelial dysfunction, atherosclerosis or insulin resistance [9]. Future research activities are needed to identify the participating signaling molecules and to clarify the exact pathophysiological relationships to develop novel drug targets and therapeutic approaches.

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**Сосудистая дисфункция и периадвентициальная жировая ткань**  
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**Резюме.** К настоящему времени расшифрованы основные механизмы регуляции сосудистого тонуса. Считается, в частности, что жировая ткань, окружающая сосуды, служит источником ADRF (adipocyte-derived relaxing factor). Важно отметить, что именно локальные паракринные расстройтва могут стать причиной сосудистой дисфункции. Наиболее вероятным кандидатом на роль ADRF называют сероводород (H<sub>2</sub>S). На экспериментальных моделях ожирения, артериальной гипертонии и метаболического синдрома доказано наличие и других соединений, участвующих в периадвентициальной регуляции сосудистого тонуса посредством влияния на калиевые каналы клеточных мембран. Вазоактивные структуры жировых клеток или их рецепторы могут оказаться перспективными мишенями для разработки новых сердечно-сосудистых препаратов.  
**Ключевые слова:** индекс массы тела, жировые клетки, вазоактивные факторы, сероводород.