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COMMENT

The usefulness of angiotensin-(1-7) and des-Arg^9-bradykinin as novel biomarkers for metabolic syndrome

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The renin–angiotensin system (RAS) and the kallikrein–kinin system (KKS) closely interact with each other [1, 2] (Fig. 1). In the RAS, angiotensinogen cleavage by renin generates angiotensin I, which is thereafter cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II. Angiotensin II then binds to the angiotensin II type 1 (AT1) receptor, resulting in the induction of vasoconstriction, inflammation, apoptosis, hypertrophy, cell proliferation, fibrosis, and oxidative stress [3]. On the other hand, angiotensin-(1-7), which is generated by the cleavage of angiotensin II by ACE2, by the cleavage of angiotensin I by neprilysin (NEP), or by the cleavage of angiotensin-(1-9) by ACE/NEP, binds to the Mas receptor and induces vasodilatation, antiinflammation, antiremodeling, antihypertrophy, antiproliferation, antiapoptosis, and antioxidation effects [3, 4]. Recently, oral administration of angiotensin-(1-7) has been reported to prevent obesity and hepatic inflammation in rats fed a high-fat diet [5]. In the KKS, kallikrein forms bradykinin (BK) from kininogen [1, 2], and BK binds to the kinin B2 receptor and induces vasodilation, nitric oxide release, hypotension, antihypertrophy, and antiischemic effects [6, 7]. Moreover, BK-induced vasodilation has been shown to be augmented by angiotensin-(1-7) in spontaneously hypertensive rats [8]. BK is inactivated by ACE (also known as kininase II) via degradation into inactive fragments [2]. On the other hand, carboxypeptidase N (also known as kininase I) metabolizes BK into des-Arg^9-BK [2, 6]. Des-Arg^9-BK binds to the kinin B1 receptor and induces vasocontraction, cell proliferation, and collagen synthesis [6, 7].

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Recently, Fernandes et al. demonstrated that angiotensin-(1-7) and BK were inversely correlated with body mass index (BMI), while angiotensin I and des-Arg^9-BK were positively correlated with BMI in adolescents, although angiotensin II did not show any correlation [9]. Moreover, while angiotensin-(1-7) and BK were inversely correlated with homeostasis model assessment, systolic blood pressure, and C-reactive protein, angiotensin I and des-Arg^9-BK were positively correlated with these parameters [9]. Additionally, although angiotensin-(1-7) was inversely correlated with triglycerides, angiotensin I and des-Arg^9-BK were positively correlated with them [9]. Interestingly, while leptin inversely was correlated with angiotensin-(1-7) and positively correlated with angiotensin I and des-Arg^9-BK, adiponectin was positively correlated with BK [9]. Based on these data, the authors concluded that angiotensin-(1-7) and des-Arg^9-BK may possibly be biological markers for adolescent obesity and therapeutic targets in the future [9]. In adipose tissues, all RAS components, including angiotensinogen, ACE, and ACE2, are locally expressed, and angiotensin I, angiotensin II, and angiotensin-(1-7) are produced in situ [10, 11]. Interestingly, adipocyte-specific ACE2 knockout female mice treated with a high-fat diet exhibited augmented obesity-induced hypertension, which was inversely correlated with the plasma angiotensin-(1-7)/angiotensin II ratio [12, 13]. Although ACE2 expression levels in visceral adipose tissues did not vary between control and obese patients [14], mouse experiments demonstrated that chronic exposure to a high-fat diet induced ADAM17 expression in adipose tissue, resulting in the shedding of ACE2 from the cell membrane of adipocytes [15]. We therefore hypothesize that the ACE2 activity in the adipocytes of metabolic syndrome patients may gradually decrease according to the duration of the condition, which may result in the reduction in angiotensin-(1-7) and the increase in des-Arg^9-BK levels (Fig. 1).

ACE2 and angiotensin-(1-7) have recently been used as biomarkers of heart failure [16, 17]. Moreover, ACE2 has been recognized as a potential biomarker of coronary heart

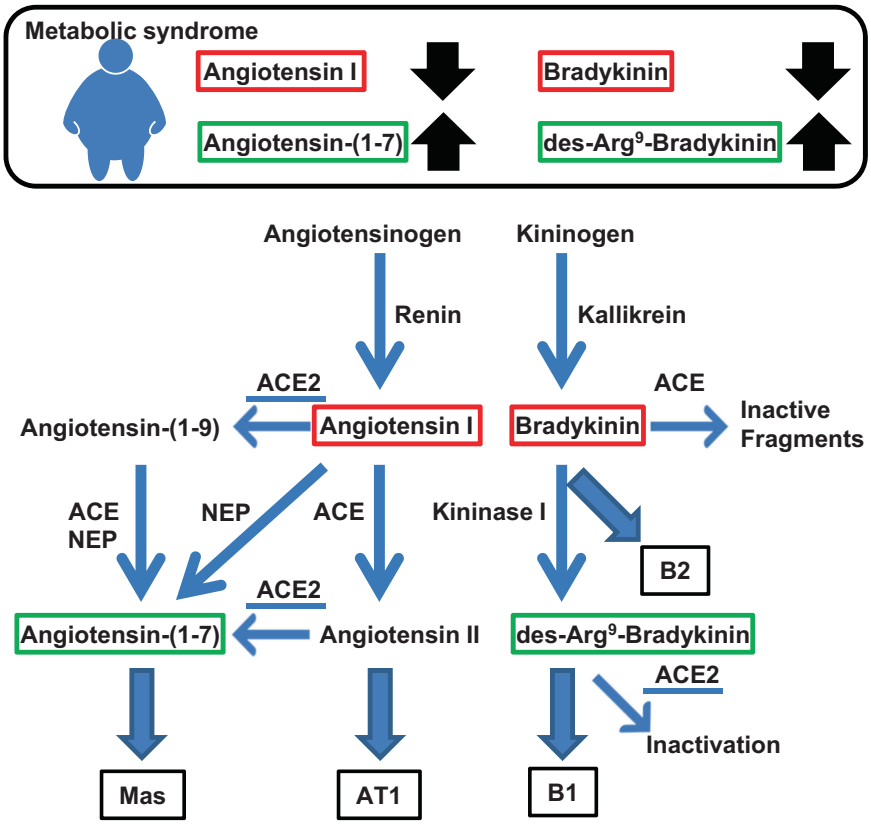

Fig. 1 Possible biomarkers for metabolic syndrome (MS) in the RAS and the KKS. Angiotensin I, ACE2, angiotensin-(1-7), BK, and des-Arg^9-BK, which are candidate biomarkers, are underlined. Markers either upregulated (↑) or downregulated (↓) in MS are indicated

disease [18]. Interestingly, angiotensin-(1-7) has also been indicated as a potential biomarker for the diagnosis of Alzheimer's disease [19]. Additionally, changes in BK and des-Arg^9-BK levels have recently been noticed as potential surrogate markers of the host response in antituberculosis treatment [20]. Although the recent study by Fernandes et al. first demonstrated the usefulness of angiotensin-(1-7) and des-Arg^9-BK as biomarkers for obesity in adolescents [9], these biomarkers may also be useful for the diagnosis of the severity of adult metabolic syndrome in the future. Further studies are needed to expand their use to adult disorders.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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