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COMMENT

Angiotensin-(1–7) as a biomarker of childhood obesity: Is there a causal relationship?

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Angiotensin-(1–7) as a product of ACE2

The renin–angiotensin system (RAS) is a major regulator of cardiovascular and metabolic systems. During the last two decades, angiotensin converting enzyme (ACE) 2-angiotensin-(1–7)-Mas was established as a counteraxis of the classical RAS pathway [1]. Angiotensin-(1–7) functionally antagonizes angiotensin II through its receptor, Mas. ACE2, identified as the homolog of ACE, plays a pivotal role in the endogenous production of angiotensin-(1–7) [2]. Substrates of ACE2 are not limited to those within the RAS and involve various peptides, including des-Arg^9-bradykinin (BK). The organ-protective role of angiotensin-(1–7) on the cardiovascular, renal, endocrine, and skeletal muscle systems has been well recognized and discussed [1].

Angiotensin-(1–7) and obesity

The favorable effect of angiotensin-(1–7) on obesity and adipose function has been well elucidated using various rodent models, including pharmacological infusion or oral intake of angiotensin-(1–7), loss of function of ACE2 or MAS, and transgenic overexpression of angiotensin-(1–7) [3]. Increased circulating angiotensin-(1–7) improved glucose and lipid metabolism and alleviated the proinflammatory profile of adipose tissue in transgenic rats overexpressing angiotensin-(1–7) [4].

Although the therapeutic effect of angiotensin-(1–7) on metabolism and obesity has been shown extensively in experimental studies, data in terms of the causal relationship between physiological levels of angiotensin-(1–7) and obesity or subsequent metabolic disorder are limited, particularly in clinical studies [5].

Obesity and fetal programming

Obesity during childhood increases the risk of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases [6, 7]. Lifestyle issues such as excess caloric intake and reduced activities as well as genetic factors clearly contribute to the development of obesity. Childhood obesity is associated with a family history of obesity and cardiovascular and metabolic diseases [8]. Recently, maternal obesity has been widely recognized as a risk factor for pregnancy complications, including gestational diabetes, preeclampsia, and delivery of large-for-gestational-age infants, which cause low or high birth weights, leading to childhood obesity and an increased risk of future cardiovascular and metabolic diseases [9–11]. Increasing evidence from experimental and clinical studies indicates that prenatal stress, including intrauterine nutrient insufficiency, hypoxia, oxidative stress, and exposure to hormones, may program the further development of diseases, which is known as fetal programming [12]. A poor intrauterine environment with maternal obesity during pregnancy is associated with higher placental vascular dysfunction and placental inflammation, which could alter placental transporter activity and mitochondrial activity [13]. A few studies have demonstrated that the mechanism of programmed obesity is associated with appetite dysregulation and adipogenesis [11]. The exact mechanisms of how fetal programming events increase the risk of obesity remain unknown and are controversial.

Obesity and angiotensin 1–7 in adolescents

Recently, Fernandes et al. revealed that plasma angiotensin-(1–7) and des-Arg^9-BK metabolites can be novel biomarkers

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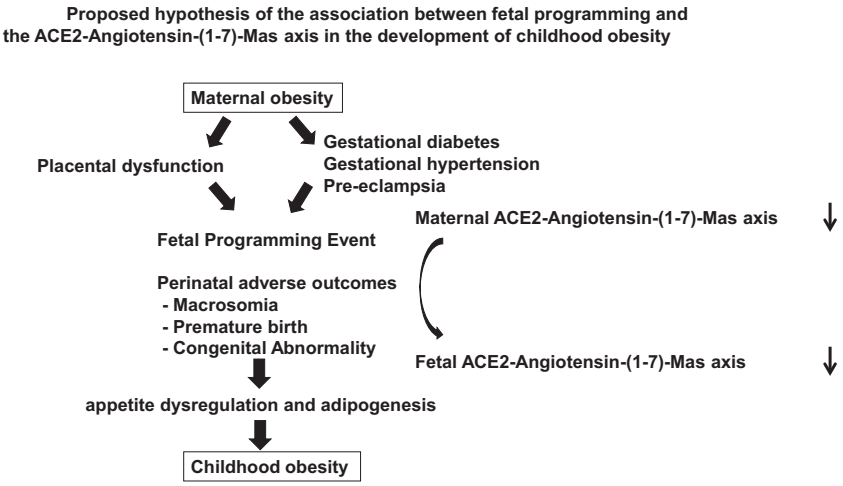

Fig. 1 Proposed hypothesis of the association between fetal programming and the ACE2-angiotensin-(1–7)-Mas axis in the development of childhood obesity

of obesity during childhood [14]. In 104 healthy adolescents aged 11–17 years without a history of hypertension and diabetes, BMI was inversely correlated with plasma levels of angiotensin-(1–7) and BK and positively correlated with angiotensin I and des-Arg^9-BK. Angiotensin-(1–7) and BK are also inversely correlated with HOMA, SBP, vasopressin, triglycerides, and CRP, suggesting relationships between the levels of these peptides and insulin resistance, hypertensive state, adiposity and systemic chronic inflammation [14]. Family history of obesity was higher in the groups with a higher BMI [14]. Given the potential favorable effect of angiotensin-(1–7) on obesity and adipose function, the authors concluded that plasma levels of angiotensin-(1–7), BK and des-Arg^9-BK are potential biomarkers that determine the degree of obesity in adolescents.

Regarding the mechanisms involved in the altered levels of angiotensin-(1–7) and BK metabolites in obese adolescents, Fernandes et al. hypothesized that ACE2 activity, as an endogenous source of angiotensin-(1–7) production and des-Arg^9-BK degradation, is reduced in obese adolescents; however, this hypothesis is inconclusive because plasma ACE2 activity was not detected in the present study [14]. Nevertheless, it should be noted that plasma ACE2 activity is not necessarily proportional to the net systemic activity of ACE2 for determining plasma angiotensin-(1–7) levels. Circulating ACE2 activity in humans may be a marker of CVD, with low levels in healthy individuals and increased levels in those with cardiovascular risk factors or diseases [15]. The classical RAS is recognized as a key signaling pathway in the pathology of fetal reprogramming, whereas a favorable impact of ACE2-angiotensin-(1–7) and Mas on fetal programming has currently been suggested [16]. Interestingly, a recent study demonstrated that preterm birth is associated with decreased fetal and maternal angiotensin-(1–7) [17]. Another study demonstrated that obesity is associated with increased angiotensin II and decreased angiotensin-(1–7) among adolescents born prematurely [18]. This could lead to a hypothesis that pathological fetal programming might attenuate the ACE2-angiotensin-(1–7)-Mas axis in the offspring to induce future pathologic conditions (Fig. 1). Nevertheless, further studies are required to elucidate the actual causal relationship between obesity and the regulation of the ACE2-angiotensin-(1–7)-Mas axis in childhood. Additionally, other molecules, including ACE and neprilysin, are also involved in the metabolism of angiotensin and BK, and further evaluation should be conducted in relation to these molecules.

Finally, ACE2 is identified as the functional receptor of SARS coronavirus (SARS-CoV-1 and SARS-CoV-2) [19, 20]. Because the recent COVID-19 pandemic is an emerging threat to global public health, the factors that regulate ACE2 expression or activities are of great interest. Given the potential involvement of ACE2 in the present study by Fernandes et al., further attention should be given to whether and how the regulation of ACE2 and its substrates would alter the health of adolescents, particularly in the context of obesity [14].

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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