糖尿病肾病专题

·综述·

柚皮苷对糖尿病肾脏疾病的作用机制

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【摘要】 糖尿病肾脏疾病(DKD)是糖尿病最严重的慢性并发症之一。目前认为 DKD 的发生、发展是多因素共同作用的结果,包括氧化应激、炎性反应、纤维化以及自噬等,而其中高血糖是最关键的,它是发生肾脏损害的先决条件。柚皮苷(4′,5,7-三羟二氢黄酮-7-鼠李葡萄糖苷)是一种从芸香科柑橘属植物柚中提取的双氢黄酮类化合物,具有多种药理活性,如抗炎、抗氧化应激、改善胰岛素抵抗、调节糖、脂代谢、抗纤维化等,可能从根本上延缓 DKD 的进展。

【关键词】 糖尿病;糖尿病肾脏疾病;柚皮苷

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【**Abstract**】 Diabetic kidney diseases (DKD) are one of the most severe chronic complications of diabetes mellitus. At present, it is thought that the development of DKD are the results of many factors, including oxidative stress, inflammation, fibrosis and autophagy, etc. Among which high blood glucose is the most critical. It is the precondition of kidney damage. Naringin (4′,5,7-trihydroxy flavonone-7-rhamnoglucoside), the major flavonoid in grapefruit juices has been shown to possess pharmacological properties such as antiinflammatory, antioxidant effects, improving insulin resistance, regulating the metabolism of glucose and fat and antifibrosis, which may cundamentally improve the process of DKD.

【**Key words**】 Diabetes mellitus; Diabetic kidney diseases; Naringin

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糖尿病肾脏疾病(DKD)是糖尿病最严重的慢性并发症之一,其发病机制复杂,目前尚不明确。已证实的机制主要包括,遗传易感性、血液动力学异常、多元醇代谢通路活化、蛋白激酶 C 激活、晚期糖基化终末产物(AGEs)堆积、足细胞损伤、氧化应激、炎性反应以及自噬等[1-4]。柚皮苷(4′,5,7-三羟二氢黄酮-7-鼠李葡萄糖苷)又称柚苷、柑桔苷,是从西柚皮中分离的一种双氢黄酮类化合物,有苦味,天然存在于芸香科植物葡萄柚、橘、橙的果皮和果肉中。柚皮苷具有多方面的药理学活性和治疗特性,其对 DKD 的作用目前尚处基础研究阶段,缺乏临床依据。下面就柚皮苷针对 DKD 发病机制的新进展作一阐述。

1 柚皮苷的降糖作用

高血糖主要通过直接作用及通过多种途径促进细胞外基质(ECM)的形成,促进并加重纤维化。同时通过多元醇途径、蛋白激酶 C、AGEs的形成等促进DKD的进展。糖基化属于翻译后蛋白修饰,是糖尿病及其他一些疾病的病理生理基础,葡萄糖在没有酶激活时,可以通过非酶促糖基化反应形成 AGEs。AGEs在细胞外聚集可广泛影响基底膜胶原Ⅳ分子间以及ECM与细胞之间的相互作用,引起结构的重塑;同时也促进了单核细胞的移动,并诱导产生生长因子和细胞因子,通过旁分泌、自分泌、内分泌途径参与DKD的病理变化。有研究指出,柚皮苷可有效减少蛋白糖基化的程度[5]。柚皮苷(100 μmol/L)

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能有效抑制AGEs的形成达40%，有望成为改善 DKD 的有效措施[6]。Kandhare等[7]发现，柚皮苷可呈剂量依赖性的降低糖化血红蛋白水平，同时改善胰岛素的分泌。但同时有实验得出相反的结论，证实柚皮苷对血糖无明显作用，如Murunga等[8]应用柚皮苷治疗链脲佐菌素（STZ）诱导的 1 型糖尿病小鼠模型，发现柚皮苷能有效改善空腹血浆胰岛素、肝糖原含量，而对空腹血糖却无明显作用。Adebiyi等[9]通过50 mg/kg柚皮苷干预Sprauge-Dawley大鼠，发现其降糖作用不明显。另有研究表示，柚皮苷虽能改善 STZ 小鼠的体重，但血糖水平同时有所上升[10]。这对柚皮苷的降糖作用提出了挑战，可能是不同的柚皮苷浓度对血糖的影响效果不同，亦或其他因素参与其中，还需更多的实验加以证实。

2　柚皮苷的抗氧化应激作用

柚皮苷是自由基的强效清洁剂，能防止脂质过氧化物的产生[11]。在真核细胞中，黄嘌呤氧化酶是超氧阴离子的生理来源，体外研究发现柚皮苷能抑制黄嘌呤氧化酶活性[12]。在糖尿病模型中柚皮苷能调节抗氧化物酶如超氧化物歧化酶（SOD）、过氧化氢酶（CAT）、谷胱甘肽过氧化物酶（GPx）[13-14]。Dhanya等[6]通过体外培养L6肌细胞时发现，用不同浓度柚皮苷（1、10、100 μmol/L）分别预处理细胞 3、24 h，发现其呈剂量依赖性抑制活性氧簇浓度；1 μmol/L柚皮苷能明显降低丙二醛的浓度，还能使谷胱甘肽恢复至正常水平。柚皮苷联合维生素 C 治疗STZ诱导的Wistar大鼠后发现，治疗组能有效改善血糖、糖化血红蛋白，升高肝、肾中己糖激酶活性，降低葡萄糖-6-磷酸酶活性和果糖 1,6-二磷酸水平，减少过氧化氢脂质，使减少的 GSH 得到逆转，显示了柚皮苷的降糖和抗氧化应激作用，从而改善DKD[13]。Ali 和El Kader[15]报道，应用柚皮苷处理 STZ 诱导糖尿病大鼠后，能显著降低血糖、过氧化氢、硫代巴比妥酸水平，增加胰岛素水平和抗氧化酶活性（CAT、SOD、GPx、对氧磷酶），从而增加抗氧化能力。Chen等[16]首次表明，瘦素诱导的p38丝裂原活化蛋白激酶（MAPK）途径的激活，导致心肌损伤、氧化应激和线粒体损伤，而柚皮苷能对抗此效应。

3　柚皮苷的抗炎作用

肿瘤坏死因子-α（TNF-α）、白细胞介素（IL）-1β、IL-6、单核细胞趋化蛋白-1 等是重要的炎性因子，在 DKD 的发生、发展中起重要作用，笔者前期研究表明，柚皮苷使TNF-α和单核细胞趋化蛋白-1 的表达明显减少，起到抗炎作用[17]。另有研究表明，柚皮苷能显著降低糖尿病大鼠血TNF-α、IL-1β、IL-6 水平，发挥强效抗炎作用[7]。同时Mahmoud等[18]亦证实，柚皮苷能改善高脂饲养和 STZ 诱导糖尿病大鼠血 TNF-α、IL-6 水平，从而达到治疗目的。Kandhare等[19]发现，STZ 诱导糖尿病大鼠后，炎性介质TNF-α 升高，应用不同浓度的柚皮苷（40、80 mg/kg）治疗，可使升高的炎性介质下降，呈现剂量依赖性。可见柚皮苷可能通过抑制促炎因子、细胞因子等的产生达到抗炎效果。

4　其他

4.1　柚皮苷的抗纤维化作用　以往研究对糖尿病引起的肾小球病变关注较多，但随着对疾病认识的加深，发现在不同程度肾小球硬化的糖尿病患者中，肾间质病变程度越轻的患者，残存肾功能越多且远期生存率越高，说明肾间质纤维化并不依赖于肾小球病变，而是作为一个相对独立的发病机制，与肾功能损害关系同样密切，可见抑制肾脏纤维化的进展可从一定程度上阻止肾功能的进一步损伤。柚皮苷对肾脏纤维化的作用目前未见相关文献报道，但柚皮苷对心脏、肺纤维化的作用已有所报道。研究发现，高血糖可通过直接作用于心肌成纤维细胞促使细胞增殖，并可通过间接作用，如上调信号分子、促进纤维化的发生、活化NADPH氧化酶使血管紧张素Ⅱ产生增加及增加氧化应激使心肌重塑，柚皮苷可通过抑制氧化应激、NADPH氧化活性，下调蛋白激酶Cβ、p38 MAPK而发挥抗纤维化作用，减少纤维化区域达67%[9]。肥胖、胰岛素抵抗、高血压和脂肪肝是心血管疾病的危险因素，研究发现，喂食低纤维高碳水化合物、高脂饮食的大鼠，体重增加，血糖调节异常，血脂、血压升高，左室肥大和纤维化，出现肝脏炎性反应，以及由于线粒体呼吸链活性异常导致的脂肪变态反应。而应用柚皮苷可使上述指标得到不同程度的缓解，有一定的抗左室肥大和纤维化的作用[20]。同时柚皮苷能通过抑制TNF-α、IL-1β活性，降低羟脯氨酸、丙二醛水平，从而增加GPx和SOD活性，抵抗雷帕霉素诱导的肺纤维化[21]。柚皮苷通过抑制炎性反应和氧化应激，减少百草枯导致的急性肺损伤和肺纤维化小鼠模型纤维化物质的沉积[22]。

4.2　柚皮苷激活自噬　研究发现，DKD大鼠的足细胞自噬不足会致大量白蛋白尿产生，溶酶体功能障碍和细胞凋亡，提示自噬有抗白蛋白尿及肾脏保护作用[23]。另有研究指出，在 DKD 大鼠模型中肾脏

的自噬功能受损,通过饮食干预能够改善肾脏的自噬功能,减轻肾损害[24]。可见在 DKD 的发展过程中自噬扮演了主要角色。柚皮苷与自噬的作用目前仅见于肿瘤相关性疾病中。在胃癌细胞中,柚皮苷治疗后可发现细胞质空泡结构和自体吞噬体的形成,同时观察到,自噬蛋白Beclin 1和LC3B与MAPK的磷酸化显著相关,柚皮苷的抗增殖作用可能体现在通过激活MAPK诱导自噬,从而抑制磷脂酰肌醇 3 激酶/蛋白激酶 B/哺乳动物雷帕霉素靶蛋白级联反应[25]。在鼠肝细胞癌中,柚皮苷可激活自噬,该过程可能通过AMP活化蛋白激酶调控,体现了柚皮苷潜在的抗癌作用是通过自噬发挥作用的[26]。

5　小结与展望

炎性反应、氧化应激和纤维化是目前 DKD 研究较多的发病机制,抗炎、抗氧化及抗纤维化是延缓或阻止 DKD 进展的本质措施。大量的研究表明,柚皮苷能抑制由高血糖产生的一系列增殖、炎性反应和氧化应激反应,可见柚皮苷能从病理生理机制方面延缓 DKD 的进展。柚皮苷与自噬的关系在一些肿瘤相关性疾病中亦有研究,但是,柚皮苷对 DKD 的治疗作用仍缺乏足够证据。因此,不断展开及深入对柚皮苷的研究,可能为柚皮苷应用于 DKD 防治提供新的依据。

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（下转第 253 页）

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(收稿日期:2016-08-25)

(上接第 241 页)

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