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二甲双胍对糖尿病肾病的保护作用及其抗氧化应激机制

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[摘 要] 高糖可以促进组织细胞活性氧(ROS)的产生，导致氧化应激，而氧化应激在糖尿病肾病(diabetic nephropathy，DN)的发生和发展中起重要作用。二甲双胍作为治疗糖尿病的一线药物，近年研究显示其除降糖作用以外，还可通过激活腺苷酸活化蛋白激酶(AMP activated protein kinase，AMPK)、磷酸化p38丝裂原活化蛋白激酶(phosphorylated p38 mitogen-activated protein kinase，p-p38MAPK)，刺激醌氧化还原酶[NAD(P)H quinone oxidoreductase，NQO1]、谷胱甘肽S-转移酶a(glutathione S-transferase-a，GSTa)、过氧化氢酶(catalase，CAT)表达，阻滞晚期糖基化终末产物(advanced glycation end products，AGEs)，减少GADPH氧化酶表达和改善胰岛素抵抗等机制发挥抗氧化应激作用，从而预防和延缓DN的发生和发展。

[关键词] 二甲双胍；糖尿病肾病；氧化应激

Metformin protects diabetic nephropathy and its antioxidation mechanism

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Abstract Hyperglycemia can promote the generation of reactive oxygen species and result in oxidative stress in vivo. Oxidative stress plays an important role in the occurrence and development of diabetic nephropathy (DN). Besides the hypoglycemic effect, metformin, as the first-line drug for the treatment of diabetes, can prevent and delay the occurrence and progress of DN through some antioxidation mechanisms, including activation of the AMP activated protein kinase (AMPK), phosphorylated p38 mitogen-activated protein kinase (p-p38MAPK), stimulate the expression of NAD(P)H quinone oxidoreductase (NQO1), glutathione S-transferase-a (GSTa), and catalase (CAT), block advanced glycation end products (AGEs), reduce the expression of GADPH oxidase, improve the insulin resistance and so on.

Keywords metformin; diabetic nephropathy; oxidative stress

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糖尿病肾病是糖尿病微血管并发症之一，也是导致终末期肾衰竭和糖尿病患者死亡的常见原因。二甲双胍现已被国内外指南一致推荐为糖尿病治疗的一线首选药物，一些研究[1-3]表明二甲双胍不仅可以降血糖，还可以明显减少糖尿病肾病(diabetic nephropathy，DN)患者的尿蛋白排泄，对糖尿病肾脏病变有一定的保护作用；机制尚不十分明确，可能与其减轻体内氧化应激有关。本文就二甲双胍的肾脏保护作用及其与抗氧化的关系作简要综述。

1 糖尿病肾病与氧化应激

研究表明高糖可以促进体外和体内多种细胞活性氧(ROS)的产生[4-5]，进而加速组织细胞的衰退和糖尿病多种慢性并发症的发生和发展，包括DN[6]。动物试验和临床研究[7-8]结果显示：在血糖控制不佳的状态下，体内过氧化物酶(catalase，CAT)和超氧化物歧化酶(SOD)水平降低，而血浆丙二醛(MDA)水平显著增高。此外，糖尿病大鼠肿瘤坏死因子α(TNF-α)、髓过氧化物酶(MPO)活性增高，转化生长因子β(TGF-β)和亚硝酸盐的含量显著增加[9]。高糖激活氧化应激、同时激活纤维化和前炎症因子，导致内皮细胞功能障碍，肾小球系膜基质的积聚，足细胞的分离和丢失，肾小球基底膜变薄，肾小管肥大，肾小管上皮细胞的空泡形成，肾小管纤维化和间质炎症[10-12]。

2 二甲双胍的肾脏保护作用

二甲双胍90%~100%在肾脏排泄，肾功能不全时其清除率减少[13]。多项研究[14-15]显示二甲双胍可改善肾小管对毒性反应的抵抗。Maheshwari等[9]用二甲双胍或辅酶Q10或二者联合使用处理STZ-烟碱所致糖尿病大鼠，发现二甲双胍或辅酶Q10联合二甲双胍组较糖尿病小鼠显示出糖化血红蛋白(HbA1C)、尿蛋白、血肌酐、尿酸水平显著减少，丙二醇和谷胱甘肽水平明显减少。二甲双胍组小鼠SOD和CAT活性明显升高，亚硝酸盐含量明显降低，脂质过氧化反应明显减少。辅酶Q10或者二甲双胍处理显示其减轻肾小球坏死，间质纤维化，减轻肾小管空泡样变性及肾小球基底膜变厚。用辅酶Q10或者二甲双胍或者联合使用可改善STZ-烟碱所致的肾损害，可以提高肾功能，改善氧化应激，抑制TNF-α，MPO活性，减少TGF-β和亚硝酸盐含量，同时显示仅轻度肾小管肿胀、肾间质纤维化和肾小球基底膜的增厚的表现，且无肾小球硬化症。Zhai等[16-17]报道：与格列本脲比较，在血糖控制相似的情况下，二甲双胍可更加有效地保护2型糖尿病大鼠肾小球足PCX和nephrin的表达，减少蛋白尿排泄。二甲双胍改善肾脏损伤的主要信号通路包括调节腺苷酸活化蛋白激酶(AMP activated protein kinase，AMPK)/mTOR(雷帕霉素)通路、内质网紊乱、上皮细胞间质转型，自我吞噬、氧化应激和糖基化终产物、低氧诱导因子(hypoxia-inducible factors，HIF)和脂毒性[18]。Zhai等[16]用高脂饮食联合低剂量链脲霉素制造糖尿病大鼠模型，并用不同剂量二甲双胍处理8周，发现相比较于T2DM大鼠，用不同剂量的二甲双胍处理后的大鼠，尿白蛋白和肾病蛋白水平、肾小球基底膜厚度和足突融合率明显改善，大鼠肾组织足细胞标志蛋白表达明显增加。由此推论，二甲双胍可通过剂量依赖方式调节2型糖尿病大鼠模型肾脏组织肾病蛋白的表达，从而保护肾足细胞。

3 二甲双胍的抗氧化作用

二甲双胍能显著降低2型糖尿患者体内氧化应激水平，从而发挥血管保护作用。糖尿病患者体内活性氧类水平增高被证实与糖尿病并发症的发生和进展有关。Chakraborty等[19]将208位Ⅱ型糖尿病患者随机分为两组，分别接受二甲双胍与安慰剂治疗，经24周的二甲双胍治疗后，相较于安慰剂组病人，晚期氧化蛋白产物较基线显著减少，而总硫醇和NO水平较基线显著增高，患者白细胞内ROS显著减少，指示二甲双胍治疗可以导致自由基介导的氧化应激减少。而二甲双胍减少氧化应激及血中胆固醇的作用，可能是其使糖尿病患者钠钾泵的活动恢复到可控水平的基础。Esteghamati等[20]将99位新诊断的T2DM患者随机分为经二甲双胍治疗和改善生活方式两组，经3个月二甲双胍治疗后，晚期糖基化终末产物(advanced glycation end products，AGEs)和晚期氧化蛋白产物(advanced oxidation protein products，AOPP)明显减少，且血清胰岛素浓度减少34%。此外，多种临床试验证实二甲双胍可减少蛋白的氧化终产物，降低AGEs和ROS水平[19-22]。Kim等[2]研究二甲双胍对SDT大鼠(一种非肥胖二型糖尿病大鼠的新模型)肾足细胞损伤的保护作用。43周糖尿病大鼠血糖和白蛋白显

著升高，肾小球结构明显改变，且尿和肾中8-羟基脱氧鸟苷(8-OHdG)水平显著升高，末端标记法和蛋白染色显示足突细胞减少。而经二甲双胍(每天350 mg/kg)治疗17周，SDT大鼠所有的肾脏改变得到修复。推论抗糖尿病药物可通过抑制氧化损伤从而减少糖尿病肾病足突细胞丢失，同时发现糖尿病小鼠足细胞密度的减少与增加的白蛋白排泄有关，且细胞外ROS是导致足细胞凋亡的有力因素。

4 二甲双胍的抗氧化机制

4.1 AMPK 信号通路

虽然二甲双胍精确的降糖机制尚有争议，AMPK信号通路的活化仍被普遍认为是二甲双胍作用的最主要的机制[23]。AMPK是一种系统发育保留的丝氨酸–苏氨酸蛋白激酶，可以作为调控系统和细胞能量状态的标准[24]，可在能量限制状态下保护细胞功能[25]。多项研究[26-29]发现二甲双胍在线粒体基质中聚集，并抑制ATP合成，增加AMP/ATP比，最终激活AMPK，AMPK作为能量传感器和代谢转换器，调节一个复杂的信号和代谢网络。AMPK信号通路活化还可通过上调抗氧化酶影响细胞内氧化还原状态[30]。Kim和同事[2]发现磷酸化的AMPK在糖尿病小鼠中减少，而二甲双胍可以修复其改变。Hou等[31]发现二甲双胍可减少暴露于游离脂肪酸的内皮细胞产生的ROS，归于其通过激活AMPK通路上调抗氧化的硫氧还蛋白的表达。

4.2 磷酸化 p38 丝裂原活化蛋白激酶 (p-p38MAPK)

在糖尿病肾病的病理改变中，p38MAPK涉及多信号转导通路，激活磷酸化p38丝裂原活化蛋白激酶(phosphorylated p38 mitogen-activated protein kinase，p-p38MAPK)可以促进细胞的增殖，生长和分化[32-33]。Yao等[34]通过细胞实验发现：相比较于正常组，大鼠肾小球细胞高糖组上清液中SOD的活性明显降低，而丙二醛的水平及p-p38MAPK蛋白表达明显增高。二甲双胍加入高糖体系中，大鼠肾小球上皮细胞上清液中SOD的活性明显增加，而丙二醛的水平、p-p38MAPK蛋白明显降低，推测二甲双胍可改善大鼠肾小球系膜因高糖导致的氧化应激和p-p38MAPK蛋白表达。Bao等[35]证实激活线粒体AMPK–沉默调节蛋白1–过氧化物酶体增殖物激活受体γ共激活因子α(AMPK–SIRT1–PGC-1α)信号通路可以缓解高脂饮食所致的糖尿病模型大鼠体内氧化应激。

4.3 抑制 AGEs 形成

慢性高血糖状态下AGEs形成增加及其在氧化应激中的作用，被证实与糖尿病并发症(包括肾病、视网膜病变和心血管疾病)相关[19]。Pang等[36]指出AGEs可以诱导细胞凋亡，而二甲双胍可以抗凋亡，其机制可能为通过激活AMPK，抑制活性氧的生成和NF-κB的激活，上调Bcl-2，下调Bax和Caspase-3表达，增高Bcl-2/Bax比值相关。Kim等[2]报道二甲双胍可通过阻滞糖基化终末产物和改善自由基防御系统，进而预防糖尿病肾病。Chakraborty等[19]从前临床阶段研究中发现，二甲双胍治疗后，AOPP和AGE减少，相比于对照组，抗氧化状态得到改善。Esteghamati等[20]用二甲双胍治疗T2DM患者3个月，致使血清晚期氧化蛋白产物和AGEs明显减少，抗氧化标志物水平增加。

4.4 醌氧化还原酶、谷胱甘肽 S- 转移酶 a 和过氧化氢酶

Alhaider等[37]发现二甲双胍治疗可明显恢复链脲佐菌素–糖尿病大鼠肾组织谷胱甘肽转移酶、NQO1、过氧化氢酶(catalase，CAT)基因表达，通过抗氧化作用发挥肾保护作用，该作用不依赖其对血糖的影响。还可阻滞TNF-α和IL-6等前炎症基因，调节线粒体的氧化磷酸化，这也是其减轻糖尿病大鼠肾实质细胞氧化应激的原因之一。

4.5 GADPH 氧化酶

MDA为自由基作用于脂质过氧化而产生的终末产物，可间接反映机体氧化损伤水平。p47phox和p22phox为GADPH氧化酶亚单位，是调控ROS产生酶的主要来源[38]。杨迪等[39]培养大鼠肾小球系膜细胞，将其分为正常对照组(NC组)、高糖组(HG组)及高糖+不同浓度二甲双胍组。与NC组比较，HG组p47phox和MCs p22phox mRNA表达显著增高，上清液中的SOD活力显著降低，且MDA含量显著增高。HG组MCs p47phox和p22phox mRNA表达显著高于二甲双胍+高糖组，且二甲双胍浓度越高，MCs p22phox和p47phox mRNA表达越低，提示二甲双胍减少糖尿病大鼠肾小球系膜细胞3-磷酸甘油醛脱氢酶(GADPH)氧化酶的表达水平，而

起到减轻氧化应激的作用。

4.6 转录因子 2(Nrf2)

转录因子2(nuclear factor erythroid-2-related factor，Nrf2)是一种氧化应激、核因子调控和调节基因表达的细胞传感器，用来保护过量ROX及细胞应激引起的细胞破坏[40]。Nrf2可通过激活抗氧化应激防卫机制，而改善大鼠糖尿病肾损害[41-42]。先前研究[43]显示上调的血红素氧合酶(HO-1)被广泛用来评估Nrf2信号的激活。Alhaider等[37]发现二甲双胍以剂量依赖的方式明显减少DN诱导的mRNA水平的HO-1，其机制为使不依赖AMPK信号通路介导的Nrf2失活[44]。

4.7 其他

研究[20,45-46]表明二甲双胍可通过改善胰岛素抵抗，间接减少氧化应激，恢复机体抗氧化应激储备。Alhaider等[37]研究显示用二甲双胍处理血糖正常的大鼠，会导致肾内生及线粒体内的ATP、乙酰CoA和辅酶A(CoA-SH)的显著增高，AMP水平的明显减少，使代谢旁路产物乙酰CoA正常化。

5 结语

综上所述，氧化应激促进了DN的发生和发展，而二甲双胍对糖尿病患者肾有一定的保护作用，部分与其抗氧化作用有关，但其机制可能是多途径的，具体的作用机制仍有待进一步研究。

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