P.O.Box 2345 Beijing 100023, China
Fax: +86-10-85381893
Email: wcjd@wjgnet.com www.wjgnet.com

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氧自由基与胃黏膜损伤

施华秀, 任建林

施华秀, 任建林, 厦门大学附属中山医院消化内科 厦门市消化疾病研究所 福建省厦门市 361004
通讯作者: 施华秀, 361004, 福建省厦门市湖滨南路201号, 厦门大学附属中山医院消化内科, 厦门市消化病研究所. huaxiu.shi@xmzsh.com
电话: 0592-2292017 传真: 0592-2292017
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摘要

我们在概述了氧自由基的概念、来源和氧自由基反应的损伤作用后, 综述了其在胃部疾病中的作用, 提示氧自由基与急性胃黏膜损害、慢性胃炎、消化性溃疡和胃癌的发病密切相关, 并阐述自由基清除剂对胃黏膜损伤的保护作用.

关键词: 氧自由基; 胃黏膜; 损伤

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0 引言

自由基指具有未配对电子的原子、原子团或分子, 由氧分子衍生的自由基称氧自由基.主要包括超氧自由基(O_2^-)和羟自由基(OH•), 它们与过氧化氢、单线态氧(O^1)统称为活性氧.

1 氧自由基的产生

据文献[1-3]报道, 人体内总自由基中约95%以上属氧自由基, 因此, 氧自由基对人体有特殊的意义, 常见的氧自由基有超氧阴离子(•O_2^-)、氢过氧基(HO_2•)、过氧化氢(H_2O_2)、羟自由基(HO•)、氧有机自由基(RO•)、有机过氧基(ROO•)、单线态氧($^1O_2$)、活性氧(ROS)、脂自由基(L•)和脂过氧基(LOO•).

正常情况下, 98%的氧还原为水, 1-2% 的氧通过单价还原形成氧自由基.造成机体的氧自由基增多的原因有两种: 外源性因素, 主要是离子辐射、紫外线照射、超声、毒物、食物、药物及污染物; 内源性因素, 包括炎症时中性粒细胞"呼吸爆发"、线粒体损伤和缺血、金属中毒等.

2 氧自由基反应的损伤作用

正常人体内存在清除氧自由基的防御系统, 使其生成量不至于达到损伤组织的程度. 机体自身抗氧化系统主要包括酶系清除系统和非酶系清除系统. 前者包括超氧化物歧化酶(SOD)、过氧化氢酶(CAT)和谷胱甘肽过氧化物酶(GSH-Px)等; 后者包括维生素E、A、C和硒, 以及半胱氨酸和谷胱甘肽等. 然而机体清除氧自由基的能力是有限的, 氧自由基产生过多时, 就会造成组织损伤[4-5].

氧自由基具有杀菌、细胞毒和促进炎性渗出、水肿等重要炎症介质作用. 由于氧自由基作用的靶细胞和分子无特异选择性, 故氧自由基在参与杀菌等防御作用的同时, 也会给组织细胞造成损伤. 幽门螺旋杆菌(*H pylori*)感染、NSAIDs、乙醇等坏死因子、缺血再灌注损伤、应激、幽门结扎等所致胃黏膜损伤的模型中, 均涉及氧自由基的作用. 可以认为, 氧自由基参与了绝大多数致溃疡因子的致病过程, 与慢性胃炎、急性胃黏膜损伤、胃溃疡和胃癌的形成有密切关系[6-8].

与其他组织的炎症相似, 胃黏膜在各种损伤因子作用下发生炎症时产生大量的炎症因子, 造成中性粒细胞浸润, 通过"呼吸爆发"产生氧自由基, 因此中性粒细胞可能是氧自由基的主要来源.胃黏液在化学物质作用或缺血等情况下, 可产生大量的氧自由基.缺血时, 黏膜细胞内氧化磷酸化减少, 三磷酸腺苷(ATP)生成减少. 有报道鼠出血休克15 min 后, 胃黏膜内ATP减少75%, 二磷酸腺苷(ADP)减少27%, 而一磷酸腺苷(AMP)增至50%, AMP可进一步代谢为腺苷、肌苷及次黄嘌呤. 很多实验研究证明, 氧自由基对缺血再灌注性胃黏膜损伤机制主要是氧自由基导致胃黏膜上皮细胞和黏膜血管内皮细胞多价不饱和脂肪酸过氧化[9-11]. 此外, 细胞能量不足时, 不能维持正常的离子梯度, 细胞内Ca^{2+}增多, 激活一种蛋白酶, 使黄嘌呤脱氢酶快速不可逆地转变成黄嘌呤氧化酶(XO).缺血黏膜中同时有XO和次黄嘌呤的聚集, 当组织再灌流时, 就可产生大量的超氧自由基.超氧自由基和过氧化氢通过Haber-Weiss反应可生成细胞毒性更大的羟自由基. 正常情况下, Haber-Weiss反应的速度非常缓慢. 当存在金属离子时, 反应速度显著加速, 即所谓Fenton型Haber-Weiss 反应. 缺血时细胞外铁水平增加, 由此可增加羟自由基的生成. 线粒体呼吸链受损和花生四烯酸代谢中也可产生部分氧自由基. 在许多种系中, 胃肠道黄嘌呤脱氢酶的含量远高于其他任何组织. 所以一旦有条件, 胃黏膜将产生大量氧自由基[12,13].

3 氧自由基与胃部疾病

3.1 急性胃黏膜损害 自从Itoh和Guth 1985年报道给予SOD和过氧化氢酶可以明显减轻缺血-再灌注引起的胃黏膜损伤以来, 进一步研究证实它们也可以减轻乙醇和NSAIDs引起的急性胃黏膜损害, 从而间接提示在急性胃黏膜损害发病过程中, ROS起了重要作用. Alarcon *et al*[14]发现给鼠动脉灌注自由基可引起胃黏膜损伤, 而SOD同时灌注可以减轻胃黏膜损伤. Yashimura *et al*[15]研究表明, 鼠胃腔灌注乙醇后胃黏膜脂质过氧化物(LPO)增加, 自由基清除剂别嘌呤醇能缓解酒精性胃黏膜损伤, 提示乙醇引起的胃黏膜损伤与氧自由基有关. Sakai *et al*[16]研究兔胃黏膜氧自由基的变化, 发现胃黏膜损伤与氧自由基有密切关系. Brzozowski *et al*[17]研究证实阿司匹林所致的急性胃黏膜病变过程中存在氧自由基反应, 黏膜组织中LPO产物丙二醛(MDA)的含量明显增高. 其他一些研究也支持上述观点, 但详细机制有待进一步研究[18-20]. 因此, 氧自由基是急性胃黏膜损害的重要致病因子.

急性胃黏膜损害时氧自由基的来源因病因不同而异: 缺血-再灌注损伤时主要来自黄嘌呤氧化酶; NSAIDs引起的胃黏膜损伤时氧自由基主要来源于白细胞; 酒精性胃黏膜损伤可能来自醛氧化酶[21-25].

3.2 慢性胃炎 *H pylori*是慢性胃炎的最主要病因之一, 但其致病机制尚不清楚, 近年来研究提示, *H pylori*致病可能同氧自由基有关. Shimoyama *et al*[26]发现*H pylori*的可溶性蛋白可刺激单核-巨噬细胞产生$\bullet O_2^-$; Shimizu *et al*[27]观察到*H pylori*提取液在引起鼠胃黏膜急性损伤的同时, 也诱发了胃黏膜MDA的明显增加, 而氧自由基清除剂可明显减轻胃黏膜损伤. Danese *et al*[28]发现*H pylori*的超声分解产物对多形核白细胞和单核细胞有趋化活性. Jung *et al*[29]发现*H pylori*的无细胞培养上清液可激活白细胞的氧爆发; 与*H pylori*阴性组比较, *H pylori*感染者胃黏膜内所有抗氧化物浓度无明显区别, 但氧反应物质化学荧光和丙二酰二醛的浓度升高, 肯定了*H pylori*阳性患者胃黏膜中存在氧自由基. Suzuki *et al*[30]研究发现感染*H pylori*的胃窦黏膜ROS明显增加, 未感染的胃窦黏膜不产生可检测的ROS, 并且ROS与*H pylori*感染相关.其他研究亦说明, ROS在*H pylori*致病中起重要作用, 激活的中性粒细胞"呼吸爆发"可能是氧自由基的主要来源[31-34].

3.3 消化性溃疡 关于氧自由基致消化性溃疡的机制, 目前认为很可能是氧自由基对黏膜的损伤作用. Lazaratos *et al*[35]发现自由基生成系亚铁离子/维生素C黏膜内注射可以诱发胃溃疡, 并且伴有脂质过氧化终末产物MDA升高, 给予SOD可以缩小溃疡面积, 降低MDA含量. Bandyopadhyay *et al*[36]利用药物诱导胃溃疡发生, 也证明氧自由基可直接损害黏膜细胞, 脂质过氧化参与胃肠黏膜损伤.

Demir *et al*[37]研究发现胃溃疡患者血清LPO含量明显高于正常对照组, 认为胃溃疡的发生与氧自由基关系较密切.食物中的超氧化物和过氧化物与铁离子结合, 通过Fenton反应产生羟自由基(•OH). •OH能引发细胞膜的脂过氧化, 产生过氧化磷脂. 而在金属离子的作用下, 过氧化磷脂又产生碱化脂或过氧化基团, 使氧化链反应进一步放大, 造成广泛的细胞膜和重要生物分子的损害和组织损伤[38-41].

氧自由基引起消化性溃疡的机制, 可能与以下两方面有关: 一是脂质过氧化损害. 氧自由基与膜内多价不饱和脂肪酸结合, 形成多种LPO, 导致生物膜多价不饱和脂肪酸与蛋白质比例失常, 影响细胞膜的流动性和通透性, 破坏膜上酶和受体功能, 形成新的离子通道, 以致线粒体有大量的 Ca^{2+}内流, 形成更多的氧自由基. 周而复始, 会使线粒体渗透转运孔开放, 其结果是线粒体膜电位不能保持, 最后造成细胞死亡, 这一过程完成大约需要60 min.

另一方面, 是共价键结合性损伤. 氧自由基作用于含巯基的氨基酸, 使蛋白质变性和酶失活; 作用于辅酶, 使辅酶活性下降; 作用于碳水化合物, 使表面受体改变. 尤其是氧自由基能破坏上皮间质中的透明质酸和胶原纤维网, 促进黏膜损伤[42-47].

3.4 胃癌 Chang *et al*[48]研究发现胃癌患者血浆与组织中LPO明显高于对照组, 并且发现胃癌组织中自由基浓度明显比对照组高, 提示自由基可能参与胃癌的发生. 流行病学调查提示, 自由基清除剂维生素C和维生素E的缺乏与胃癌发生有关, 补充维生素C可减少胃黏膜中DNA损害[49-51].

4 自由基清除剂对胃黏膜损伤的保护作用

4.1 预防性抗氧化剂 包括抗氧化酶和金属络合剂、SOD、CAT、GSH-Px等. SOD是理想的清除自由基的抗氧化剂, 但由于半衰期极短, 且不稳定, 限制了它的临床应用. 研究报道[52-57], 自由基清除剂别嘌呤能促进溃疡愈合, 明显降低溃疡的复发率. 含SH的化合物有清除自由基的作用, 研究证明氧化型的SH化合物如硫糖铝有促进溃疡愈合, 防止复发的作用. 此外, 某些中药成分如银杏内酯A能明显减轻束缚水浸应激引起的大鼠胃黏膜溃疡的产生, 其抗溃疡作用也可能和减少自由基产生和增加其清除有关.

4.2 连锁反应阻断剂 包括水溶性抗氧化剂谷胱甘肽、维生素C、葡萄糖等, 脂溶性抗氧化剂维生素E、类胡萝卜素、甘露醇等.

瑞巴派特(rebamipide)是一种新的黏膜保护药, 通过抗氧化作用对多种氧自由基产生损伤的动物模型具有抗损伤保护作用; 促进胃黏膜内源性PG的合成释放,

保护胃黏膜, 增加胃黏膜血流量, 从而对溃疡的发生和发展产生抑制作用, 减少溃疡的发生[58].

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