

超氧化物歧化酶参与肝损伤的研究进展

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[摘要] 目的:介绍超氧化物歧化酶(SOD)参与肝损伤的研究进展。方法:查阅国内外相关研究资料并对其进行汇总、分析和综述。结果:SOD 及其分型参与肝损伤多种模型的病理过程。结论:在肝损伤的病理过程中,SOD 起重要作用;深入开展肝损伤模型及药物保肝研究,需要考察 SOD 及其分型。
[关键词] 超氧化物歧化酶;肝损伤;研究进展
[中图分类号] R285.5 [文献标识码] A [文章编号] 1005-9903(2011)07-0265-05

Research Progress of Superoxide Dismutase Involved in Liver Injury

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[Abstract] Objective: To introduce the research progress of superoxide dismutase (SOD) involved in liver injury. Method: Consulted the related medical journals, analyzed and compiled them. Result: SOD and its types participate in the pathological process of many types of liver injury. Conclusion: SOD plays an important role in the pathological process of liver injury. SOD and its types should be paid adequate attention to in deep studies of animal models and protective action.
[Key words] superoxide dismutase; liver injury; research progress

[收稿日期] 20101120(006)

[基金项目] 国家自然科学基金(30772794,30701082);国家重点基础研究发展(973)计划(2006CB504704);河南中医学院博士科研基金(BSJJ2010-22)

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生物体内的能量代谢将氧气作为有氧代谢过程中的电子接受体,不可避免地产生活性氧(reactive oxygen species, ROS)自由基。机体 ROS 具有双重效应,与某些生理活性物质的调控和炎症免疫过程密切相关,但是过量的 ROS 容易导致氧化应激状态^[1]。线粒体呼吸链复合体利用电子传递生产三磷酸酰酐(ATP),是 ROS 的主要来源^[2],肝脏含有丰富的线粒体,因此也是最容易受 ROS 攻击的器官。ROS 引发的氧化应激是多种类型肝损伤发病的共同的病理生理基础之一。SOD 作为体内清除 ROS 自由基中的超氧阴离子

(O_2^-) 的专一性的抗氧化酶,在肝损伤的研究中具有异常重要的作用。鉴于此,本文就 SOD 在肝损伤研究中的应用进行综述,以期对肝损伤相关的研究提供理论依据。

1 SOD 简介

SOD 广泛存在于生物体中的重要金属结合酶,SOD 家族是唯一将超氧阴离子转化为过氧化氢的抗氧化酶。目前已知的哺乳动物体内 SOD 有 3 种异构体^[3],分别是 CuZn-SOD、Mn-SOD 和细胞外超氧化物歧化酶 (EC-SOD 或 SOD3)。CuZn-SOD 主要存在于哺乳动物细胞的胞浆、胞核及溶酶体、过氧化物酶体内。Mn-SOD 主要存在于需氧细胞的线粒体中。EC-SOD 是 1982 年 Marklund 等^[4]首先在动物血浆中发现的,在人体中主要分布在组织外基质和细胞表面上,是细胞外液如血浆、淋巴液、关节液及脑脊液中最主要的 SOD 同工酶,其本质也是 CuZn-SOD,是清除细胞外 O_2^- 的主要酶。98% 以上的 EC-SOD 结合在细胞表面和结缔组织基质中的硫酸乙酰肝素上。因为 O_2^- 难以穿过细胞膜,3 种 SOD 主要在它们各自的部位发挥保护功能。

2 SOD 参与肝损伤的研究进展

2.1 酒精性肝损伤 酒精性肝损伤是指长期或大量饮含有乙醇的饮料造成的肝脏疾患,是常见的导致肝硬化的原因。近年来我国酒精性肝损伤的发病率明显增加,日益引起社会及医学界的高度重视。氧化应激被认为是酒精性肝损伤最重要发病机制之一,在酒精性肝损伤的形成和发展过程中起重要作用。SOD 作为体内唯一的 O_2^- 清除剂,参与酒精性肝损伤的病理过程。

Liu 等研究发现,与正常大鼠比较,酒精性肝损伤大鼠的原代肝细胞 SOD 活力明显降低^[5],而槲皮素可逆转 SOD 的降低,一定程度上增加了 O_2^- 的清除,从而起到保肝作用;另有研究发现,酒精性肝损伤动物肝 SOD 活性明显降低^[6-8],而经栀子大黄汤或葛根提取物或白杨素干预后,其 SOD 活性均显著升高,同样增加了 O_2^- 的清除,肝功能明显恢复。此外,研究还发现,酒精性肝损伤动物肝组织 CuZn-SOD 和 Mn-SOD 的 mRNA 和蛋白表达比正常动物均明显降低^[9-11],提示 CuZn-SOD 和 Mn-SOD 缺乏是酒精性肝损伤的发病机制之一。

2.2 四氯化碳 (CCl_4) 肝损伤 CCl_4 进入机体后,经肝脏细胞色素 P450 激活,生成三氯甲基自由基 ($\cdot CCl_3$) 和三氯甲基过氧自由基 ($\cdot OOCCL_3$),这 2 种自由基引起肝细胞的各种变化导致肝损伤。虽然 SOD 不能直接针对这两种自由基,但可清除 O_2^- ,对损伤起到一定的缓解作用。大量研究表明^[12-21],不管是急性、亚急性还是慢性 CCl_4 肝损伤,动物肝的 SOD 活性均明显降低,而给以诸如肉桂醇提物、沙棘种子油、草苈蓉环烯醚萜苷等药物干预后,SOD 活性明显逆转,增加了 O_2^- 的清除,有的损伤可恢复至正常水平。

2.3 二甲基亚硝胺 (DMN) 诱发的肝损伤 DMN 是常见的致癌剂,它通过微粒体代谢,其中间产物与细胞核酸、蛋白质等结合致肝损伤,同时产生一种活性甲基化产物使核酸、

蛋白质甲基化导致肝坏死。研究表明,SOD 缺乏会加剧 DMN 诱发的肝损伤,而一些保肝药物可通过增强 SOD 活性增加了 O_2^- 的清除从而对 DMN 所致的肝损伤有治疗作用^[22]。

2.4 D-半乳糖胺 (GalN) 诱发的肝损伤 GalN 是一种肝细胞毒性药物,可在短时间内引起严重肝损害。研究表明,GalN 诱发的肝损伤模型动物肝内 SOD 明显降低,一些保肝药物可对其逆转^[23-24]。

2.5 药源性肝损伤 肝脏是药物在体内代谢的最主要场所,是最容易遭受药物影响的脏器^[25]。由于各种药物的广泛应用,药源性肝损伤已经成为严重的健康问题^[25]。氧化应激是许多药源性肝损伤的机制之一。SOD 在氧化应激中清除 O_2^- 的专有作用,决定了其在药源性肝损伤的研究中异常重要的作用。

研究发现,对乙酰氨基酚 (acetaminophen, PAPA)、甲氨喋呤、顺铂、胺碘酮、硝苯地平、米诺环素、呋喃西林、雌激素、它莫西芬、异烟肼、雷公藤甲素、黄药子等药物均可诱发药源性肝损伤,引起动物肝 SOD 活性降低^[26-33],给以药物干预后可对其逆转,表明 SOD 可作为药源性肝损伤氧化应激性指标广泛应用。另有研究表明,Mn-SOD mRNA 敲除后,PAPA 诱发肝损伤加剧^[34],提示 PAPA 诱发的肝损伤与 Mn-SOD mRNA 缺乏有关。

2.6 其他类型肝损伤 研究发现,在非酒精性肝损伤、缺血再灌注性肝损伤、免疫性肝损伤、二氧化碳气腹肝损伤、氯化镉诱发的肝损伤、放射性造影剂诱发的肝损伤等模型动物肝内 SOD 活性均降低,一些药物可对其逆转^[35-45]。研究表明,非酒精性肝损伤模型动物肝 CuZn-SOD mRNA 表达与正常动物没有差异;研究发现,缺血再灌注肝损伤模型动物肝 Mn-SOD mRNA 表达明显升高^[46-47]。

3 SOD 参与保肝的主要机制

当生物体处于复杂的内外环境中,体内会不断地产生自由基。自由基是含有未成对电子的化学性质活泼的原子或原子团、分子或离子,其中对机体有特殊意义的是活性氧,它是指氧自由基及其衍生物,主要包括 O_2^- 、羟自由基 ($\cdot OH$)、过氧化氢 (H_2O_2)、其衍生物单线态氧及脂类过氧化中间产物等。大量证据表明失衡的、高浓度 ROS 具有细胞毒作用,导致细胞内关键成分损伤,如 DNA、蛋白质、脂质损伤^[48],参与多种疾病的发展过程,如:各种肝病、肿瘤、高血压、糖尿病、炎症等。

为保护机体免受过氧化损伤,需氧生物有一套酶促与非酶促抗氧化防护系统,可以最大限度地降低由此产生的致病效应。其中,抗氧化酶防御系统主要包括 SOD、过氧化氢酶 (CAT)、还原型谷胱甘肽 (GSH)、谷胱甘肽过氧化物酶 (GPx) 和谷胱甘肽-S-转移酶 (GST) 等^[49]。其中 SOD 存在于有氧代谢的细胞内,构成体内第一道抗氧化酶防御体系,其功能是清除 O_2^- ,也是体内唯一清除 O_2^- 的抗氧化酶。

SOD 催化 $O_2^{\cdot -}$ 的反应如图 1 所示(GSSG 为氧化型谷胱甘肽)。

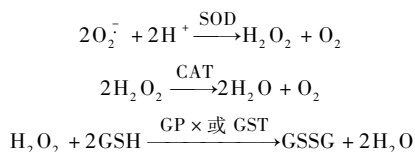


图 1 SOD 催化 $O_2^{\cdot -}$ 的反应

从图 1 可知,SOD 作为机体的第一道抗氧化防御系统的主要执行物质,对肝损伤的恢复起到了关键作用。当肝脏受到过多的 $O_2^{\cdot -}$ 袭击时,肝脏的 SOD 一方面会直接清除过多的 $O_2^{\cdot -}$,从而有助于肝损伤的修复;另一方面,SOD 还可以与机体内的第二道乃至更多的抗氧化防御体系有机的配合,最终可起到预防肝损伤或修复肝损伤的作用。

4 结语

SOD 作为一种人体内最重要的酶之一,它所起的作用是不可小视的。正常生命过程中产生的 $O_2^{\cdot -}$ 是维持肝脏功能所必需的,当其受到过高浓度 $O_2^{\cdot -}$ 攻击时,对肝脏会造成损伤。SOD 作为体内唯一的 $O_2^{\cdot -}$ 清除剂,在治疗氧化应激肝损伤中具有异常重要的作用。SOD 几乎用于所有类型的肝损伤模型,并在许多保肝药物研究中广泛应用。除此之外,SOD 在参与肝损伤研究中还有以下几个特点或作用。① 酒精性肝损伤、药源性肝损伤均与肝内 Mn-SOD 活力、基因及其蛋白表达降低有关。② 由于 Mn-SOD 主要位于线粒体,而线粒体又是氧损伤的主要靶细胞器,由此决定了 Mn-SOD 在抗氧化酶中的特殊地位,许多类型的肝损伤均与 Mn-SOD 的异常相关。③ 开展肝损伤,尤其是药源性肝损伤研究,不仅要关注总 SOD,更要关注其分型 Mn-SOD。综上所述,深入开展肝损伤模型及药物保肝机制研究,应具体到各分型 SOD 的活性、基因及蛋白的研究,以阐明其作用机制。

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红外光谱技术在中药炮制研究中的应用与展望

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[摘要] 随着红外光谱技术的应用及化学计量学等新技术的发展,红外光谱法成为中药分析的有力工具和手段。红外较强的鉴别能力、准确的测定结果和快速的响应功能,使其在中药炮制研究中的应用逐渐扩大。该文综述了近 10 年来国内外红外光谱技术在炮制研究中的发展与应用,并对其存在问题 and 应用前景进行了讨论。

[关键词] 近红外;中红外;炮制;应用;展望
[中图分类号] R284.1 [文献标识码] A [文章编号] 1005-9903(2011)07-0269-03

Application and Prospect of Infrared Spectroscopy in
Chinese Medicine Processing

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[Abstract] With the application of infrared spectroscopy and chemometrics and other new technologies, infrared spectroscopy becomes a powerful tool in traditional Chinese medicine. Its strong ability to identify, accurate results and fast response measurement capabilities, make its application expanding gradually in the study of

[收稿日期] 20101127(002)
[基金项目] 国家自然科学基金面上项目(81073041);高等学校博士学科专项科研基金(20100013120010)
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