世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2011年12月28日; 19(36): 3666-3671
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

葡聚糖硫酸钠结肠炎模型影响因素的研究进展

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■背景资料
溃疡性结肠炎(ulcerative colitis, UC)动物模型以化学药物诱导结肠炎为主, 而葡聚糖硫酸钠(dextran sulphate sodium, DSS)结肠炎模型与人体UC表现最相似, 目前国内UC动物模型主要以DSS应用最广.

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上海市科研基金资助项目, No. 08cz017
国家自然科学基金资助项目, No. 30873261
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收稿日期: 2011-08-27 修回日期: 2011-11-20
接受日期: 2011-12-18 在线出版日期: 2011-12-28

Factors influencing the development of animal models of dextran sulphate sodium-induced colitis

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Supported by: the Scientific Research Foundation of Shanghai Municipal Education Commission, No. 08cz017; and National Natural Science Foundation of China, No. 30873261
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Received: 2011-08-27 Revised: 2011-11-20
Accepted: 2011-12-18 Published online: 2011-12-28

Abstract

The animal models of dextran sulphate sodium (DSS)-induced colitis have demonstrated several correlations with human ulcerative colitis (UC) since the first report of DSS-induced colitis in hamsters in 1985. These animal models have similarities to human UC in etiology, pathology, pathogenesis and therapeutic response, and are deemed suitable for investigating the pathogenesis and therapeutic options of UC and UC-related dysplasia-adenocarcinoma sequence. Although induction of colitis with DSS is relatively cheap and simple, the development of this model is influenced by many factors, such as DSS concentration, administration duration, DSS molecular weight and animal species. These factors are important for successful development of DSS-induced colitis. In this paper we summarize factors influencing the development of animal models of DSS-induced colitis.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Dextran sulphate sodium; Influencing factors

Wen HZ, Hao WW, Li J, Tang ZP. Factors influencing the development of animal models of dextran sulphate sodium-induced colitis. Shijie Huaren Xiaohua Zazhi 2011; 19(36): 3666-3671

摘要

自1985年首次报道采用葡聚糖硫酸钠(dextran sulphate sodium, DSS)制备出仓鼠溃疡性结肠炎模型以来, 已有大量研究证明DSS结肠炎模型与人类溃疡性结肠炎相似. 该模型的病因、临床症状、病理改变及治疗应答均与人类UC相类似; 对于研究UC病因、发病机制及UC相关增生和肿瘤, 确定治疗手段有重要意义. 虽然DSS模型制作简单; 但该过程受到多个因素的影响: DSS浓度、给药时间、DSS相对分子质量和动物种属等. 如不能正确处理这些因素, 很难制造出成功的DSS结肠炎模型. 本文主要针对DSS造模影响因素及尚需我们进一步研究和探讨的问题作综述如下.

关键词: 炎症性肠病; 溃疡性结肠炎; 葡聚糖硫酸钠; 影响因素

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http://www.wjgnet.com/1009-3079/19/3666.asp

0 引言

葡聚糖硫酸钠(dextran sulphate sodium, DSS)结肠炎模型的组织学特点、临床表现、发病部位和细胞因子增殖情况都与人类溃疡性结肠炎(ulcerative colitis, UC)极为相似. 该模型的造模条件和操作方法简单, 造价便宜, 重复性好, 便于掌握和推广; 可根据实验目的调整DSS浓度和给药时间, 建立急性、慢性和急慢性交替性模型, 可模拟慢性UC及其易复发特性; 还可根据需要

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建立UC相关直肠结肠肿瘤模型, 这些都是其他模型所无法比拟的. 但其造模成功与否与多种因素有关, 实验中如不能妥善把握这些因素, 则难以成功建立DSS模型. 影响DSS造模的因素主要包括DSS浓度、给药时间、DSS相对分子质量(molecular weight, MW)和动物种属. 基于这些影响因素在DSS造模中的重要地位, 我们主要针对DSS造模影响因素及尚需我们进一步研究和探讨的问题作综述如下.

1 DSS造模现状

炎症性肠病(inflammatory bowel disease, IBD)主要包括UC和克罗恩病(Crohn disease, CD); 该病常见于欧美国家, 近年来在我国的发病率也逐渐升高, 但其确切病因至今仍未阐明, 一般认为与现代生活方式、环境污染以及感染、遗传和免疫等多个因素有关, 这就增加了在人体中研究IBD的难度; 故目前一般采用动物模型研究IBD的病因、发病机制和临床治疗. 迄今为止, IBD的动物模型研究历史已有一百多年, 虽然近年来已经研发出了多种采用基因敲除和转基因技术制造的基因型IBD模型[1-9]; 但因其造价昂贵、制作复杂, 较难推广. 故当前国内IBD研究仍以化学药物诱导结肠炎为主, 如三硝基苯磺酸(TNBS), 该模型炎症时间长, 慢性炎症表现突出, 组织学改变与人类CD尤其相似[10,11], 目前在国外使用较广; 因TNBS模型与UC表现相差较远, 而国内以UC为主, 所以其在国内的适用性不强. 目前国内UC动物模型主要以DSS应用最广.

2 DSS造模机制、方法和表现

2.1 DSS DSS是一种由蔗糖合成的、有抗止血和抗凝血作用的肝素样硫酸多醣体, 分子式为$(C_6H_7Na_3O_{14}S_3)n$, MW 5 000-1 400 000不等, 含硫量一般为16%-20%. DSS为白色粉末状物, 室温保存, 极易溶于水(100 mg/mL). DSS结肠炎模型由日本学者Ohkusa[12]于1985年首次制造成功. 随后Okayasu等[13]于1990年在小鼠中成功建立了DSSUC模型. 而慢性仓鼠UC模型由Yamada等[14]于1992年首次报道. 自此以后针对DSS动物结肠炎的研究如火如荼, 大部分研究者[12-19]就DSS动物结肠炎模型的症状和肠道改变与人类UC相似这点基本达成共识; 还有研究者直接将DSS结肠炎模型称为DSSUC模型.

2.2 DSS诱导结肠炎的机制 自DSS结肠炎模型首次建立到现在, 已就DSS模型发病机制开展了大量研究, 但其确切机制仍尚未明确. 目前的研究主要认为可能与DSS增加肠道通透性、破坏肠黏膜屏障、上调某些细胞因子、激活某些通路或肠道菌群失调等有关[20-34]. Kitajima等[20]的研究发现DSS可引起肠道通透性增加, 从而诱导炎症反应的发生; Verdu等[21]及Poritz等[22]的研究也支持这一观点. Ni等[23]的研究则认为DSS通过对结肠黏膜细胞的直接毒性作用起效. Verdu等[21]及Kokešováa等[28]的研究表明予DSS结肠炎小鼠正常肠道菌群可缓解动物的结肠炎症状; 但考虑到DSS结肠炎模型可在无菌动物(Germ Free, GF)中造模成功, 因此认为肠道菌群在DSS发病机制中的作用不是非常重要. 此外, 还有大量研究证实Th1细胞, NF-κB通路和TRPV1通路, TNF-α、IFN-γ和IL-4等细胞因子在DSS诱导结肠炎中起着重要作用.

2.3 造模方法 通常采用在蒸馏水(纯水)中加入DSS制成DSS溶液给予动物自由饮用造模, 浓度采用W/V计算. 采用不同的DSS溶液浓度、给药时间和给药频率, 可制成急性和慢性两种结肠炎模型. 一般来说, 急性结肠炎模型常采用相对高浓度的DSS溶液、相对短的给药时间建立. 如予小鼠2%-5%DSS自由饮用4-7 d[35-43]. 上海中医药大学脾胃病研究所采用予BALB/c小鼠5%DSS(MW为40000)自由饮用7 d, 成功制成了急性UC模型[44]. 慢性结肠炎模型则可采用低浓度DSS建立, 但给药时间较长. 如予仓鼠1%DSS自由饮用100 d[14]. 予大鼠1%DSS自由饮用6 mo[45]. 此外, 还可采用相对高浓度的DSS周期给药建立. 如予小鼠2.5%DSS自由饮用7 d, 随后予水自由饮用7 d; 治疗2个周期建立慢性结肠炎模型[46]. 予大鼠4%DSS自由饮用6 d, 随后予水自由饮用6 d; 治疗3个周期建立[47]. 结肠炎相关结直肠肿瘤模型则可采用低浓度DSS周期给药建立, 但目前可用的相关报道较少. Darren等[48]报道予小鼠0.7%DSS自由饮用7 d, 随后予水自由饮用10 d; 治疗12个周期制成结肠炎相关结直肠肿瘤模型. Chang[49]和Cooper[50]等则采用4%DSS给药4 d, 随后予水自由饮用17 d, 重复3-4个周期建立结肠炎相关肿瘤模型. Clapper等[51]报道采用DSS和偶氮甲烷同时给药建立结肠肿瘤模型.

2.4 DSS结肠炎表现 DSS结肠炎的症状表现包括腹泻、黏液样便、粪便潜血阳性、肉眼血便、动物体质量下降、进食量减少、活动度减弱、毛色变差、贫血, 甚至死亡等. 这些症状与人类UC极为相似. 急性期最早出现的症状为粪便潜

■研发前沿
进一步明确DSS造模的影响因素(主要为DSS浓度、给药时间、DSS相对分子质量和动物种属)在UC模型建立中的重要作用, 对于UC实验研究有重要指导意义.

■相关报道
Shimizu等发现动物结肠黏膜隐窝损伤程度与DSS浓度和造模时间呈正相关, Kitajima等报道40000相对分子质量DSS的结肠炎最严重, 各种属动物造模情况不同.

血阳性和腹泻, 最早可见于造模第2-3天; 此后随着造模时间的延长而逐渐加重. 慢性期为腹泻、血便逐渐停止、体质量增加并可恢复至发病前水平. 急性期炎症反应一般局限在结肠部位, 肉眼改变包括结肠充血、水肿、变短, 变脆等. 光镜下组织病理学改变主要为全结肠多灶性小溃疡, 主要侵及黏膜层, 也可侵至黏膜下层和黏膜肌层; 黏膜水肿、杯状细胞缺失、隐窝肿胀变形破坏; 黏膜和黏膜下层炎症细胞浸润, 包括中性粒细胞、巨噬细胞、浆细胞和部分淋巴细胞. 慢性期则以上皮增生、黏膜纤维化和淋巴结肿大为特征; 同时可见肉芽组织增生和肿瘤样改变[13,52]. 虽然可在DSS结肠炎模型中观察到回肠形态学改变, 但DSS一般对小肠无影响[53].

3 影响DSS造模的因素

已有多项研究证明DSS诱导的炎症发病和严重程度主要与DSS浓度、给药时间、MW和动物种属4个因素有关. 以下将按照造模影响因素逐点选取有代表性的文献, 进行分析阐述.

3.1 DSS浓度 根据文献报道, 可采用0.5%-10%浓度的DSS造模[13-16,35-42]. 因为肠黏膜急性损伤的程度与DSS浓度呈正相关[54], 所以增加给药浓度则应相应的缩短给药时间; 浓度过高时, 动物的死亡率也会增加. 分析文献发现实验中以3%和5%两个浓度最常用. 我们研究所一般采用5%浓度造模[44]. Shimizu等[54]予4周龄大鼠2%、3%和4%浓度的DSS液自由饮用, 结果发现大鼠的临床表现和结肠组织学变化随DSS浓度的增加(2%-4%)而加重. Egger等[55]的研究也证明DSS诱导的黏膜损伤程度主要取决于DSS浓度, 而不是动物摄取的DSS总量. 研究者将56只BALB/c小鼠分成4组, 分别予0%、2.5%、5%、7.5%的DSS液自由饮用7 d, 观察各组的黏膜隐窝损坏程度及促炎性细胞因子的表达情况, 结果发现结肠黏膜隐窝损伤评分随DSS浓度的增加而增加, 促炎性细胞因子的表达也增加. 而Granger等[56]的研究发现, 只要小鼠摄入的DSS量超过某一定值(30 mg/g体质量), 即可建立重复性和可靠性均较好的小鼠结肠炎模型. 总之, DSS诱导结肠炎症的临床表现和黏膜损伤程度呈DSS浓度依赖性; 且小鼠摄入DSS总量≥30 mg/g体质量时, DSS总摄入量的差异不会影响造模结果. 但尚未确定其他种属动物的关键总剂量.

3.2 给药时间 DSS结肠炎症随造模时间延长加重, 甚至可导致动物死亡. 但目前尚无针对每种DSS浓度的最长给药时间(造模成功且动物死亡率在可接受范围内)报道, 实验中一般根据预初实验结果及文献报道数据制定给药时间. 如我们研究所根据反复试验摸索出5%造模浓度的最佳给药时间为5-7 d[44]. 已有大量文献报道DSS结肠炎症与造模时间呈正相关. 如Iba等[57]报道予4%DSS自由饮用, 大鼠的结肠损伤评分随时间延长升高. Gaudio等[47]予SD大鼠自由饮用4%DSS溶液, 结果提示DSS结肠炎症进展呈时间依赖性. 给药第3天时, 大鼠出现黏液血便, 组织病理学主要表现为基底部1/3的隐窝破坏; 第4天时, 隐窝进一步被破坏, 伴有轻度中性粒细胞浸润; 第5天时, 动物出现广泛的炎症反应, 结肠黏膜糜烂, 肠上皮细胞增生; 第6-7天时, 结肠黏膜出现多发性溃疡, 重度中性粒细胞、淋巴细胞和浆细胞浸润.

3.3 DSSMW 根据相关研究报道, 主要认为DSSMW与模型的病变严重程度及病变部位有关, 目前多采用MW在36000-50000间的DSS造模[58-63]. 但目前可用的DSSMW与造模情况的相关性研究较少, 且有些研究结果相矛盾, 仍需更多的研究进一步明确DSSMW与造模的关系. Kitajima等[64]给予BALB/c小鼠5%DSS(MW分别为5000、40000和500000)自由饮用7 d造模, 结果发现结肠炎最严重的为40000造模组, 病变主要位于远端结肠; 其次为5000造模组, 病变主要位于近端结肠; 而500000造模组无结肠炎表现. 但也有研究表明[55]DSS结肠炎模型与DSS剂量无关. 而Hirono等[65]采用3种MW(9500、54000和520000)的2.5%浓度的DSS溶液予ACI大鼠自由饮用, 研究不同MW的DSS的致癌性, 结果表明54000的致癌活性最高, 而MW为520000和9500的DSS无显著致癌活性.

3.4 动物种属 DSS模型可采用小鼠、大鼠、仓鼠和豚鼠造模, 但各种属动物对DSS易感性、临床表现、炎症严重程度和病变部位不同. 根据文献报道, 对DSS治疗最敏感的动物为豚鼠[66]. 仓鼠、豚鼠和WD大鼠的病变部位主要见于右半结肠[66-68]. Fischer 344大鼠、BALB/c和CBA/J小鼠的病变部位主要见于左半结肠[13,68]. Swiss-Webster小鼠的病变部位则主要见于中段结肠[36]. 这些差异可能与遗传差异有关, 但尚缺乏研究进一步证实以上观点. 此外, 同一种属不同品系动物的易感性和病变部位也不同. 例如: 最早用于建立小鼠DSS结肠炎模型的为BALB/c小鼠, 但2006年有研究[59]发现C57BL/6小鼠结肠炎的

炎症严重程度甚于BALB/c小鼠. Sasaki等[69]的研究也证实了该结论. Michael等[70]研究了9种品系(C3H/HeJ、C3H/HeJBir、C57BL/6J、DBA/2J、NOD/LtJ、NOD-scid、129/SvPas、NON/LtJ和NON. NOD-H2g)的小鼠对DSS治疗的易感性. 结果发现C3H/HeJ、C3H/HeJBir、NOD/LtJ和NOD-scid小鼠对DSS治疗极为敏感, 而大部分NON/LtJ小鼠对DSS治疗不敏感. C3H/HeJBir、C3H/HeJ、NOD/LtJ和NOD-scid小鼠盲肠和结肠病变几率相似; 而C57BL/6J和129/SvPas的病变部位主要位于结肠. 因为不同种属小鼠饮用相同浓度的DSS溶液炎症情况不同, 研究者因此提出可能是先天性遗传决定了不同品系小鼠的抗炎症损伤能力, 而发现小鼠的这些易感基因也许能找出相应的分类基因、指导人类IBD疾病的治疗方案.

3.5 其他 除了上述影响因素外, 动物年龄也是重要因素之一. 在造模动物年龄选择上, 一般多选择成年动物, 一方面是因为幼年动物处于生长期, 体质量增加可能掩盖DSS给药诱导的体质量下降; 另一方面是出于幼年期动物各系统尚未完全发育, 耐受能力较差考虑. 我们研究所总结多年经验认为建立小鼠DSS结肠炎模型时, 以≥18 g(6-8周龄)小鼠最佳.

4 结论

DSS结肠炎模型是目前最理想的UC模型, 其造模成功与否主要与DSS浓度、给药时间、MW和动物种属有关. 虽然已经有专家针对上述4个影响因素开展独立的研究, 但仍需更进一步阐明这些因素及其他因素与DSS造模间的确切关系; 如DSSMW与造模间的关系, DSS含硫量与造模间的关系等. 因此, 对于DSS造模因素的研究还有待我们进一步深入和探讨. 此外, 目前也尚未有对这4个因素开展的综合研究, 从而得出一个最佳动物种属、最佳DSS浓度和最佳给药时间的组合, 这不仅需要有一个良好的实验设计, 还需要有统计学家的积极参与; 此类研究具有一定的难度, 但克服困难进一步深入探讨DSS造模的影响因素具有很大价值和意义.

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■创新盘点

本文系统综述了DSS UC造模中的影响因素, 重点介绍了DSS浓度、分子量、给药时间以及动物种属和品系对UC造模的影响, 并首次提出了含硫量可能对造模也存在影响的观点; 这类综述报告极少.

■应用要点
DSS结肠炎模型是目前最理想的UC模型，且因造模条件和操作方法简单，造价便宜，重复性好等优势，在实验中应用最广.

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■同行评价
文章选题新颖, 实用性强, 对指导UC实验研究工作有重要参考价值.

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