肝纤维化动物模型造模方法的研究进展*

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摘要:肝纤维化是肝脏受到损伤后细胞外基质合成、降解与沉积不平衡的一种修复反应。对肝纤维化进行早期诊断、早期治疗,预防肝硬化的发生、发展,对肝病患者的生命质量具有重要的意义。而肝纤维化动物模型的建立,既可深入全面地研究肝纤维化发病机制,又可为临床筛选防治肝纤维化药物提供基础研究。通过对常用的肝纤维化动物模型造模方法的阐述,为肝纤维化的基础实验研究和临床治疗提供参考。

关键词:肝纤维化;动物;模型

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Study on Producing Methods of Animal Model of Hepatic Fibrosis*

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ABSTRACT: Hepatic fibrosis is a response to repair of unbalance between synthesis, degradation and deposition in the extracellular matrix after liver injury. Early diagnosis and treatment is of significance for preventing hepatic fibrosis and hepatic cirrhosis development as well as for improving life quality of hepatopath patients. The establishment of animal model of hepatic fibrosis can not only research pathogenesis of hepatic fibrosis deeply, but also provide basis for clinical medicine choice of preventing hepatic fibrosis, which will offer reference for basic research and clinical treatment of patients with hepatic fibrosis.

Key words: Hepatic Fibrosis; Animal; Model

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前言

任何可引起肝损伤的因素长期、反复作用于肝脏,均可产生肝细胞变性、坏死,继而肝细胞再生和纤维组织增生,导致肝纤维化,严重时发展为肝硬化、肝癌等[1]。随着研究的不断深入,人们对肝纤维化的发生机制有了更深的认识,有研究者明确提出肝纤维化甚至肝硬化有可能逆转的观点[2,3]。因此,探讨制备肝纤维化动物模型的方法,以期建立与各种原因所致人类慢性肝病相似的肝纤维化动物模型,深入全面地研究肝纤维化发病机制,为临床筛选防治肝纤维化药物提供研究基础。本文就目前常用的肝纤维化动物模型造模方法作一综述,为肝纤维化的基础实验研究及其治疗方案提供参考。

1 化学性损伤肝纤维化模型

化学性肝纤维化是由肝毒性的化学物质引起的慢性肝脏损害的结果。造模应用的药物有四氯化碳(CCL4)、二甲基亚硝胺(DMNA)、D-氨基半乳糖(DGA)、二乙基亚硝胺(DEN)、硫代乙酰胺(TAA)等。

1.1 CCL4诱导的大鼠肝纤维化模型

CCL4是氯化烷烃类化合物,可直接溶解肝细胞膜,经肝细胞细胞色素P450依赖性混合功能氧化酶的代谢,生成活性的三氯甲基自由基和氯甲基自由基,启动脂质过氧化作用,导致肝细胞损伤。用CCL4攻击建立的肝纤维化模型,具有简便、易行、价廉、耗时短、病变典型等特点,目前被广泛使用。

1.1.1 单纯CCL4法诱发大鼠肝纤维化模型[4] 一般采用40%~60% CCL4橄榄油溶液,有经口服、灌胃、蒸气吸入、皮下注射和腹腔注射等方法造模。造模时间依给药的途径2~4月不等。用橄榄油将CCL4配制成40%油剂,首次按5 ml/kg体重对大鼠皮下注射,以后3 ml/kg体重注射,3天一次,共42天,肝纤维化形成。该造模方法简单、易行,但死亡率较高。

1.1.2 CCL4联合苯巴比妥制备肝纤维化模型[5-8] 该方法基于CCL4在肝内经混合功能氧化酶作用形成三氯甲基自由基,启动脂质过氧化作用损伤肝细胞,而苯巴比妥作为药酶的诱导剂,可增加细胞色素P450的活性,从而增加CCL4的毒性作用。该方法1969年首先由Mclean使用,于饮水中加入苯巴比妥(35 mg/dl),加CCL4蒸气吸入。以后逐渐改进为CCL4灌胃或口服并辅以苯巴比妥为唯一饮用水的方法建立肝纤维化动物模型,可死亡率仍在40%左右;也有研究者采用CCL4联合苯巴比妥钠及食用白酒进行诱导造模,缩短了造模周期,死亡率12.86%。

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1.1.3 CCL4 复合法制备大鼠肝纤维化模型[9,10] 采用高脂低蛋白食物(以玉米面为饲料,加0.5%胆固醇,实验第1,2周加20%猪油),30%酒精为唯一饮料,皮下注射CCL4(第1次用0.5ml/100g体重,以后每隔3天皮下注射40%油剂CCL4 0.3ml/100g体重),实验第4周形成肝纤维化。该造模方法简单易行,病变有明显分期,形成率高(100%),死亡率低(20%)。

1.2 DMNA 诱导的肝纤维化模型[11-15]

DMNA 是常见的肝毒剂。它通过肝微粒体代谢,其中间产物与核酸、蛋白质等结合致肝细胞损伤,同时产生的活性甲基化产物使核酸、蛋白质等重要的生命物质发生甲基化反应,细胞外基质进行性增加,肝细胞坏死。常用的造模方法是用1% DMNA 按1ml/kg生理盐水稀释液腹腔注射,每周前3天给药,每天1次,持续3周,第4周仅在周一给药1次,4周后大鼠肝纤维化形成。该模型造模周期短,死亡率低,形成的肝纤维化相对稳定,多用于研究不同细胞外基质的产生部位,评价肝纤维化血清标志物的可靠性等,但由于该药是致癌物,实际操作中须慎用。

1.3 DGA 诱导肝纤维化模型[16]

DGA 诱发动物肝损害与人类急性肝炎相似。通过促进内毒素产生,激活 Kupffercell,导致一系列炎性因子释放,促进活性氧产生,引起肝氧化增强,代谢紊乱,造成肝细胞内某些代谢产物缺乏,诱发药物性肝炎。造模一般用10% DGA 盐水稀释液,以250ml/kg体重腹腔注射小鼠,每周6次,约半年形成肝纤维化。该模型耗时长,药品昂贵,多用于肝纤维化的可逆性研究。

1.4 DEN 诱导肝纤维化动物模型[17,18]

DEA 可通过与 DNA、RNA 及许多蛋白质结合,造成 DNA 损伤,影响 RNA 转录。用0.01% 二乙基亚硝胺诱发大鼠肝纤维化模型中,经过非特异性坏死期、肝纤维化期、肝细胞非典型增生期、肝癌期几个过程。二乙基亚硝胺广泛存在于食物中,可诱发多种动物肿瘤。大鼠所诱发的肿瘤多为肝细胞瘤,与人肝细胞癌比较相似。二乙基亚硝胺同样具有致癌性,实验中须慎用。

1.5 TAA 诱导肝纤维化模型[19-21]

TAA 在肝内代谢成硫氢化合物,与肝大分子物质结合,阻碍 RNA 从细胞核到细胞质的转移,进而影响依赖酶的代谢过程,同时还能激活磷脂酶 A2,引起肝细胞膜损害,肝细胞坏死。肝实质的破坏引起间质内结缔组织的生成增多,从而引起纤维组织在局部的沉积。一般 TAA 用生理盐水配制成30%溶液,作为实验动物的饮用水,8周形成肝纤维化。TAA 的毒性大,易挥发,排泄物在24小时内含有毒性,易污染环境,故此造模方法需慎用。

2 酒精性肝纤维化动物模型[22,23]

肝脏是酒精代谢、降解的主要场所。过度饮酒是导致人类肝纤维化的主要因素之一。在代谢过程中,自由基产生和脂肪积蓄及脂质过氧化均可对肝细胞造成损伤,导致肝细胞脂肪变性、坏死,纤维组织增生,最终引起肝纤维化。然而在造模的过程中遇到的最大困难是大鼠厌酒,不能控制其摄入量,于是有研究者采用液体食物、植入人工胃管、食用白酒代替医用乙醇或改实验动物为狒狒(动物来源紧缺、价格昂贵,实验周期长,推广比较困难)等诱发肝纤维化。

3 免疫性损伤肝纤维化模型[24,25]

免疫性肝纤维化是各种原因导致慢性肝损伤的过程中,机体免疫调节紊乱,在肝脏门静脉汇管区出现免疫复合物沉积,引起血管炎和血管周围炎,并将肝星状细胞激活转变为纤维细胞,同时激活肝脏内一些免疫细胞释放免疫调节因子和细胞因子,引发一系列的病理改变,导致肝组织内纤维组织的形成增多,降解减少,形成肝纤维化。国内研究者多采用人血清白蛋白、猪血清给大鼠皮下注射,并对比了大、小不同剂量组大鼠肝纤维化形成的时间及死亡率。

4 胆管结扎性肝纤维化动物模型[26-28]

结扎胆总管人为造成肝外胆道梗阻,引起梗阻部位以上胆管扩张,肝细胞浆内胆色素沉积,肝细胞变性坏死,毛细胆管淤阻、胆栓形成,汇管区胆管扩张,小胆管增生,纤维组织增生,小叶改建。将 Wistar 大鼠予以麻醉后,结扎胆总管并切断,远端结扎,发现胆总管结扎7天细胞凋亡增加,肝细胞淤阻,纤维组织增生,胆栓形成;14天细胞凋亡达到高峰,汇管区周围肝细胞变性,纤维组织增生向肝小叶内扩展;又有研究者比较了单纯胆管结扎、胆管结扎后切断和逆行性注入 TH 胶胆管粘堵造成的胆管阻塞,结果表明胆管粘堵法比其它两种方法更稳定。该模型肝纤维化形成快,自发逆转率低,但由于胆汁过度淤积而死亡率高(30%~50%),被认为是一种能模拟人肝纤维化的较理想的动物模型,主要用于考察药物的直接抗肝纤维化作用及用于筛选非创伤性肝纤维化血清指标等研究。

5 营养性肝纤维化动物模型[29]

通过膳食不平衡或缺乏特种营养素(低胆碱性膳食、维生素E及胱胺酸缺乏等)而引起肝细胞脂肪变性,进而形成纤维化。采用胆碱缺乏食物饲喂大鼠,成功复制了营养性肝纤维化模型,12-24周肝纤维化形成。该模型与人的酒精性肝病相似,较适用于人类酒精中毒性肝纤维化的研究,但耗时长,饲料配制复杂,花费大,单用此法造模者少。

6 血吸虫性肝纤维化模型[30,31]

血吸虫虫卵及虫卵肉芽肿分泌成纤维细胞刺激因子,刺激成纤维细胞增殖、合成胶原的功能,白蛋白合成受抑制,刺激肝脏形成肉芽肿。有研究者分别用小鼠和新西兰兔感染日本血吸虫尾蚴,形成肝纤维化。该模型可用来研究血吸虫病肝纤维化的防治。

7 其它肝纤维化动物模型

根据造模的研究目的、动物不同等因素,实验研究者建立了其它的肝纤维化动物模型。如放射性肝纤维化动物模型[32]、病毒性肝纤维化动物模型[33]、金属离子摄入性肝纤维化动物模型[34]、转基因肝纤维化动物模型[35]等;还有给猪喂食黄磷[36]、树鼩人乙型肝炎病毒感染[37]等建立的肝纤维化动物模型等。

8 展望

由于肝纤维化病因的多样性,以及人与动物的种属差异等因素,建立一个造模方法简单、模型形成率高、动物死亡率低、价格低廉、病理改变呈阶段性进展、与人肝纤维化发病机制相似、可持续复制的肝纤维化动物模型,仍然是目前实验研究和临床研究中的焦点之一。虽然有些动物模型与人肝纤维化发病机制相似,但实验动物不感染人类肝炎病毒,临床上常见的肝炎后肝纤维化动物模型难以复制,严重阻碍了对乙型肝炎病毒分子生物学及所致疾病防治的研究。因此,应加强病毒性肝炎所致肝纤维化病因、病理的研究,建立能客观、真实反映人类肝纤维化的发病机理、肝炎病毒参与和诱导的动物模型,为肝炎引起的肝纤维化治疗带来划时代的意义。

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技术对纯化的酶结晶进行结构研究,以确定酶的底物结合中心和催化活性中心的结构,从而根据这些结构特征设计抑制剂。

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