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文献综述 REVIEW

大鼠肝性脑病模型的研究进展

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■背景资料
肝性脑病(HE)是急慢性肝病基础上发生的以脑神经功能障碍为主要表现的代谢紊乱性疾病, 世界消化病学会将肝性脑病分为A、B、C 3种类型, 其发病机制尚未明确, 防治也无特效疗法. HE动物模型的建立对于探知其发病机制、寻求诊断和治疗的手段发挥着十分重要的作用, 其中以大鼠模型应用最为广泛.

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Progress in developing rat models of hepatic encephalopathy

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Abstract
Hepatic encephalopathy is a serious complication of acute and chronic liver diseases and has a high mortality rate. The pathogenesis of hepatic encephalopathy remains unclear, and there is no means of prevention or effective cure for the disease. Therefore, there is an urgent need for the basic and clinical research of hepatic encephalopathy to elucidate its pathogenesis. The development of animal models is important for elucidating the pathogenesis of hepatic encephalopathy and providing new avenues for diagnosis and therapy of the disease. Among a variety of animal models, rat model is applied most widely for similarity to humans, repeatability, reliability, applicability, controllability, simplicity and economy. In this paper, we briefly review various rat models of hepatic encephalopathy that have different origins.

Key Words: Hepatic encephalopathy; Animal model; Rat

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摘要
肝性脑病是急慢性肝病较严重的并发症, 死亡率很高, 其发病机制尚未明确, 防治也无特效疗法, 因此对肝性脑病的基础和临床研究十分迫切. 肝性脑病动物模型的建立对于发病机制、诊断和治疗的研究发挥着非常重要的作用, 目前制备肝性脑病动物模型的动物种类较多, 其中大鼠模型具有与人类相似性, 良好的可重复性、可靠性、适用性、可控性、易行性和经济性等优势, 应用最为广泛. 本文就常用不同病因大鼠肝性脑病模型的制备方法和研究进展作简要综述.

关键词: 肝性脑病; 动物模型; 大鼠

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0 引言
肝性脑病(hepatic encephalopathy, HE)是在急慢性肝病基础上发生的脑神经功能紊乱. 世界消化病学会将HE分为3种类型: A型为与急性肝衰竭相关的HE, 不包括慢性肝病伴发的急性HE; B型为不伴内在肝病的严重门体分流, 并通过肝脏活检提示肝组织学正常, 此型不易被确诊, 且较少见; C型为慢性肝病、肝硬化基础上发生的HE, 无论其临床表现是否为急性[1]. HE发病机制尚未完全阐明, 也无有效的防治手段, 且严重影响患者的生活质量和生存期, 因此HE长期以来一直是国内外研究的热点. 动物模型的建立是HE研究的基础, 随着生物技术的发展, 检测、治疗技术的提高, 动物模型也有了相应的改进和发展, 其中以大鼠模型应用最为广泛, 本文就3种类型HE常用大鼠模型的建立和研究进展作一综述.

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1 A型HE大鼠模型

A型HE大鼠模型主要通过硫代乙酰胺(thioacetamide, TAA)、四氯化碳(carbon tetrachloride, CCl_4)、*D*-氨基半乳糖(*D*-galactosamine, *D*-GaIN)/脂多糖(lipopolysaccharide, LPS)、酒精诱导的肝毒性损伤、对乙酰氨基酚(acetaminophen, PAPA)、肝血流阻断及部分或全部肝切除等方法建立[2].

1.1 TAA诱导的A型HE大鼠模型 TAA诱导的急性肝衰竭大鼠模型常见的给药方式有350 mg/kg连续3 d腹腔注射、200 mg/kg皮下注射1次、300 mg/kg连续2 d灌胃等[3-5]. TAA被肝脏摄取后, 经肝细胞内的细胞色素P450混合功能氧化酶代谢成为TAA-硫氧化物, 进而引起脂质过氧化反应和肝细胞损伤, 并可直接作用于肝细胞DNA、RNA和蛋白质合成酶产生毒性作用, 以及诱导肝代谢紊乱, 而致肝坏死[6-8]. 在此类模型中, 血脑屏障是完整的, 但作为气体形式的氨仍能渗入血脑屏障, 与谷氨酸在谷氨酰胺合成酶的催化下转变为谷氨酰胺, 后者具有增加渗透压的作用, 并通过氧化应激和线粒体的渗透性改变等方式致星形胶质细胞水肿, 进而影响神经调节功能[9]; 此外TAA尚通过改变脑组织对精氨酸、鸟氨酸、赖氨酸等氨基酸的摄取指数, 引起脑代谢异常[10]. TAA制备的A型HE具有良好的可重复性, 已被国际广泛的接受, 而且具有成模时间短, 成功率高, 其肝损伤与人类肝损伤具有相似性的特点[11,12].

1.2 CCl_4诱导的A型HE大鼠模型 制备CCl_4诱导的急性肝损伤大鼠模型常用CCl_4溶于橄榄油或精制植物油, 配制成40%的浓度, 给药方式有2.5 mL/kg灌胃、1 mL/kg腹腔注射、2 mL/kg皮下注射等[13-15], 观察时间点常取6、12、24、48 h及1 wk. 对于CCl_4肝毒性的作用机制, 目前较为公认的是自由基形成及其引发的链式过氧化反应, CCl_4经肝微粒体细胞色素P450代谢激活, 生成活性自由基(CCl_3O_2•和Cl•)及一系列氧化活性物质, 与肝细胞质膜或亚细胞膜脂质发生过氧化反应, 降解膜磷脂, 破坏细胞膜完整性, 使其通透性增加, 致肝细胞坏死[16,17]. 大脑对三磷酸腺苷有高度的依赖性, 大部分细胞能量是通过氧化磷酸化获得的, 这一过程需要各种存在于线粒体内膜特殊结构上的呼吸酶复合体的参与, CCl_4就是通过抑制呼吸酶复合体Ⅰ、Ⅱ、Ⅳ而影响组织代谢的[18].

1.3 *D*-GaIN/LPS诱导的A型HE大鼠模型 将*D*-GaIN溶于生理盐水配制成100 g/L的溶液, *D*-GaIN单独制备急性肝损伤模型, 常用剂量为500、800或1 000 mg/kg腹腔注射, 联合LPS制备急性肝损伤模型常用剂量为*D*-GaIN 250 mg/kg、LPS 100 mg/kg或*D*-GaIN 500 mg/kg、LPS 50 mg/kg等, 观察时间一般为24-48 h[19-23]. *D*-GaIN致肝损伤的机制中比较经典的观点认为*D*-GaIN在肝细胞内代谢, 与鸟苷酸结合形成鸟苷二磷酸半乳糖, 后者在肝细胞内聚集, 此种结合的速度大大超过了鸟苷酸合成的速度, 导致鸟苷酸耗竭, 进而使依赖其进行合成的核酸、蛋白质、脂质等物质减少, 阻碍细胞器和酶的再生, 使细胞器受损[24,25]. *D*-GaIN联合LPS在肝脏使库普弗细胞(Kupffer cells, KCs)过度激活, 后者释放细胞因子, 介导炎症级联反应, 这种机制在急性肝衰竭模型的形成过程中所起的重要作用正在受到特别的关注[26,27]. 在此类模型中发现脑星形胶质细胞足突突起水肿, 突起周围轴突和树突水肿. Dixit和Chang发现大脑皮层及小脑的水肿和上述表现同时存在, 且有不同程度的脑组织坏死和血脑屏障破坏, 脑水肿限于灰质, 但上述改变与观测到的人类相应变化不全相符, 该类模型常应用于诱发电位的研究[2,28].

1.4 乙醇诱导的A型HE大鼠模型 常用50%-60%的乙醇4 g/kg灌胃或6 mL/kg腹腔注射的给药方式建立酒精性肝损伤模型, 观察时间为1-2 wk[29,30]. 乙醇对肝组织损害的主要机制为: 在脱氢酶的催化下生成乙醛, 后者为高反应活性因子, 与蛋白结合形成乙醛-蛋白加合物, 这种加合物不但直接损伤细胞, 而且可作为新抗原诱导免疫反应, 致使细胞受到免疫攻击[31]; 乙醇在微粒体氧化系统代谢中产生活性氧对损害组织并促使三羧酸循环障碍而影响脂肪代谢; 上述各种活动均不同程度地激发了免疫炎症反应, 炎细胞浸润、各种细胞因子释放, 进一步加重组织损伤[32,33]. 乙醇除通过损伤肝脏, 造成各种毒物未经灭活大量入脑而损伤脑组织, 尚有直接的神经毒性, 通过降低硫胺(维生素B_1)利用酶的活性, 减少硫胺含量, 从而损伤脑组织[34]. 出现情感的认知、执行能力、知觉、判断力和视觉能力下降, 反应时间延长, 步态和平衡均受到影响等结果[35].

1.5 PAPA诱导的A型HE大鼠模型 PAPA又名扑热息痛, 为常用的解热镇痛药, 造模剂量一般为300-600 mg/kg, 一次性腹腔注射, 也可为3 g/kg灌胃, 观察时间通常为24 h[36-38]. PAPA经P450代

■相关报道

Dixit和Chang发现大脑皮层及小脑的水肿和脑星形胶质细胞足突突起水肿, 突起周围轴突和树突水肿同时存在, 且有不同程度的脑组织坏死和血脑屏障破坏, 脑水肿限于灰质, 但上述改变与观测到的人类相应变化不全相符, *D*-GaIN/LPS诱导的A型HE大鼠模型常应用于诱发电位的研究.

■创新盘点
本文首次较为全面地对各种病因的肝性脑病大鼠模型进行综述, 并从造模方法及时间, 对肝脏和脑组织损伤的机制, 适用于何种研究, 优缺点等方面进行阐述.

谢成活性产物*N*-乙酰-对-苯醌亚胺(*N*-acetyl-p-benzoquinone imine, NAPQI), 后者的灭活需还原型谷胱甘肽的参与, 当NAPQI生成过多而谷胱甘肽不足时, NAPQI与细胞内大分子共价结合成加合物, 诱发氧化应激反应, 造成过氧化损伤, 并与线粒体结合扰乱细胞内能量代谢, 以及致使生物膜发生脂质过氧化, 终致肝细胞坏死[39,40]. 此外PAPA诱导的急性肝衰竭可产生亚低温, 而后者与脑组织谷胱甘肽的代谢, 血氨浓度、脑水肿程度、促炎症反应细胞活动及脑病进展密切相关[41].

1.6 肝血流阻断、部分或全肝切除制备A型HE大鼠模型 肝血流阻断、部分或全肝切除分别通过阻断门静脉、肝动脉和切除部分或全部肝脏来制备急性肝损伤模型[42-44]. 由于24 h死亡率较高, 不利于疗效的观察, 从而限制了这些模型的应用. 近来有学者提出先使用药物诱导损伤, 然后采用部分肝叶结扎切除, 保留中毒肝组织的方法, 既避免了创面过大造成大量出血而死亡, 又符合肝细胞大量坏死导致肝衰竭的机制, 其HE症状和病理变化是渐进性的, 适合疗效的观察[45,46]. 此类模型中氨大量聚集于脑内, 使谷氨酰胺合成过多, 导致脑水肿, 从而引起一系列大脑血流和内稳态的变化[47]. 目前此类模型也正被广泛推广和使用.

对于A型HE模型的建立期望达到如下标准: 可复制性, 并易于观察分期; 症状的进展包括脑水肿及其并发症(颅内高压及脑疝); 潜在的可逆转性; 脑内氨、谷氨酰胺增加; 肝脏、脑组织的病理变化具有特征性; 对实验人员具有最小的毒性和感染性[2]. 但几乎没有模型能达到以上标准, 所有的模型均有低体温、低血糖及其他系统并发症, 因此需要强调控制好体温、血糖, 及对其他系统进行检测, 并同时给予一些支持治疗[2,48].

2 B型HE大鼠模型

B型HE强调了门体分流的重要地位, 他代表了门体性脑病的纯粹类型. 由于其相对于临床并不多见, 有学者甚至质疑单纯门体分流是否足以导致脑病, 直到第11届世界消化病学会正式将此种类型独立划分出来. 其模型通过门腔静脉吻合术(portacaval anastomosis, PCA)[49,50]或胆管结扎(bile duct ligation, BDL)而建立. 端-侧PCA术式主要为结扎门静脉近端, 将门静脉和下腔静脉之间进行端-侧吻合[51]. 侧-侧PCA术式为将门静脉和下腔静脉之间进行侧-侧吻合, 其中端-侧PCA在B型HE中应用较广泛, 肝功能障碍限于肝萎缩, 中央静脉周围肝细胞损伤. PCA普遍应用于研究门腔静脉分流的效果, 考察肝储备能力的下降. 门腔分流引起脑组织中氨和谷氨酰胺增高, 改变昼夜生物节律, 使运动功能、记忆和学习能力减退, 反射下降, 降低脑的葡萄糖利用率, 改变多种神经递质功能, 与肝硬化患者出现的轻微型HE相似. 此种模型对氨非常敏感, 易造成重度昏迷[2,52].

BDL通过结扎胆总管达到肝损伤的目的[53,54]. 其机制可能与结扎胆管后继发胆管上皮细胞增生, 后者作为胆汁性肝损伤的启动因素和中心病理环节, 通过继发一系列脂质过氧化反应, 介导α-平滑肌肌动蛋白、转化生长因子β1、血小板衍生生长因子β、Ⅰ型胶原等的表达而实现[55,56]. 此类模型通过提高海马区肿瘤坏死因子-1、5-羟色胺的表达, 降低脑源性神经营养因子的表达, 从而引起认知和行为能力的异常[57,58].

3 C型HE大鼠模型

C型HE即传统意义上的HE, 其临床表现与B型相似, 并具备B型所没有的肝硬化的症状和体征, 通常C型HE已发展到肝硬化期, 并建立了完备的门体侧枝循环. 目前大多数学者认为肝功减退可能为脑病发生的主要因素, 循环分流起着次要作用, 两者有协同作用. 大鼠模型常见于CCl_4和酒精等药物引起的慢性肝损伤. 常用40%的CCl_4酒精1-2 mL/kg以及50%-60%的酒精4-6 mL/kg灌胃8 wk以上[59-62]. 目前国内外广泛应用该类模型进行生理生化指标及药品疗效的测试[63,64].

4 结论

B型和C型HE大鼠模型期望达到的标准为: 慢性肝病伴门体分流; 脑病的症状从轻微型HE到重度HE呈现阶段性; 脑病昏迷阶段Ⅱ型星形胶质细胞增生; 血氨、脑组织氨、谷氨酰胺升高; 存在促发因素; 可作为临床药物效果观察[2]. 目前HE的病理生理研究已达到细胞分子水平, 不断研究得益于模型的制备. 对HE模型的研究有选用犬、小型猪及兔[65-70]. 相比之下, 大鼠模型具有价格低廉, 成功率高, 具有良好的可重复性、应用广泛等特点. 但目前仍迫切需要稳定的C型HE大鼠模型, 以及肝移植后的神经精神紊乱的模型.

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■应用要点

肝性脑病动物模型的建立对于发病机制、诊断和治疗的研究发挥着非常重要的作用. 通过对不同病因大鼠肝性脑病模型的肝脑损伤机制的阐述, 可以更加完善对该病的认识并能指导临床诊断和治疗. 本文更为肝性脑病的实验研究提供了重要的参考.

■同行评价
本文全面地分析了各种肝性脑病动物模型的建立方法及现状, 为肝性脑病动物实验的开展提供指导.

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