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综　述

抗抑郁剂氟西汀诱导肝损伤的研究现状及策略

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【摘　要】 氟西汀是目前广泛应用的抗抑郁药，用药治疗过程中可引起肝炎、皮肤病、性功能障碍、嗜睡、头晕等不良反应，然而目前对其诱导的不良反应的临床前实验研究涉及面较窄，主要集中在对氟西汀诱导的大鼠肝损伤及对其减毒研究方面，致毒机制涉及氧化应激、炎性反应、细胞凋亡等，然而具体机制迄今为止依然不清楚。现对氟西汀诱导肝损伤的致毒机制及其减毒策略的研究进行综述，以提供文献支持和思路启发，助力氟西汀的安全用药进程。

【关键词】 肝损伤；氟西汀；性别差异；致毒机制；减毒研究
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Current research status and strategies of antidepressant fluoxetine induced liver injury

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【**Abstract**】 Fluoxetine is currently a widely used antidepressant, which can cause adverse reactions such as hepatitis, skin diseases, sexual dysfunction, drowsiness, dizziness, etc. during the treatment process. However, the preclinical experimental research on its induced adverse reactions is currently limited. The preclinical experimental research on adverse reactions induced by fluoxetine mainly focuses on the study of fluoxetine induced liver injury in rats and its reduction in toxicity. The toxicity mechanism involves oxidative stress, inflammatory response, cell apoptosis, etc. However, it is still unclear to date. This article reviews the research on the toxic mechanism and detoxification strategies of fluoxetine induced liver injury, in order to provide literature support and inspiration for the safe use of fluoxetine.

【**Key words**】 Liver injury; Fluoxetine; Gender difference; Toxicity mechanism; Reducing-toxicity study

氟西汀是目前临床应用最为广泛的选择性 5-羟色胺再摄取抑制剂，可选择性地抑制 5-羟色胺转运体，阻断突触前膜对 5-羟色胺的再摄取，延长和增加 5-羟色胺的作用，从而产生抗抑郁作用[1-3]。然而，氟西汀在临床用药过程中也会诱发肝炎、皮肤病、性功能障碍、嗜睡、头晕、呕吐恶心、便秘、排尿困难、头痛、口干、水肿、腹泻、蛋白尿、血压升高、癫痫、幻听、脱发等诸多不良反应[4-20]。然而，当前对氟西汀诱导的不良反应的临床前实验研究尚不全面，主要涉及针对肝损伤及性功能障碍相关的临床前实验研究，其中尤以肝损伤及对其减毒的研究较为多见[21-30]。本文主要探索近年来关于氟西汀在诱发肝损伤及其减毒的临床前实验研究方面的最新进展，并基于现状提出研究对策，为氟西汀诱导肝损伤的致毒机制及其减毒策略的深入研究提供较系统的文献支持和思路启发，助力氟西汀的安全用药进程。

1　氟西汀诱导肝损伤的研究现状

1.1　氟西汀诱导肝损伤的临床前实验研究现状　Inkielewicz-Stepniak[21]考察了氟西汀对大鼠肝功能的影响，研究结果显示，给予雄性 Wistar 大鼠氟西汀(8、24 mg/kg)口服 1 个月后，高低 2 个剂量均引起了大鼠丙氨酸氨基转移酶(ALT)和天冬氨酸氨基转移酶(AST)显著升高，并呈现出明显的剂量依赖关系，提示氟西汀在既定剂量下口服给药引起了大鼠肝损伤；进一步分析显示，氟西汀诱导的肝损伤涉及介导的自由基反应，且氟西汀在代谢过程中不会释放 F^-，并且不会影响血清或尿液中 F^- 的生理水平。

Zlatkovic 等[22]考察了氟西汀对慢性隔离和对照大鼠肝脏的影响，研究结果显示，给予雄性 Wistar 大鼠氟西汀(15 mg/kg)腹腔注射 21 d，引起了慢性隔离和对照大鼠血清 ALT、AST 水平的显著升高，并呈现出明显的剂量依赖关系；进一步肝组织病理分析显示，氟西汀给药引起了慢性隔离和对照大鼠的肝脏中性粒细胞浸润，这是对组织损伤或细胞应激的早期反应，加之氟西汀给药还引起了单个肝细胞坏死(局灶性坏死)，这些证据一并表明，氟西汀长期给药引起了慢性隔离和对照大鼠的

肝损伤。

综上可知,氟西汀诱导肝损伤的临床前实验研究中所用动物主要为雄性 Wistar 大鼠,给药途径既有口服也有腹腔注射,氟西汀以 8 mg/kg 或 24 mg/kg 剂量口服给药 1 个月,或以 15 mg/kg 剂量腹腔注射 21 d 均可诱发雄性 Wistar 大鼠明显的肝损伤。然而,氟西汀分别对小鼠和雌性大鼠是否同样会诱发肝损伤、是否存在性别差异,以及其致毒机制为何,这些均是后续需要关注、研究以澄清的问题。

1.2　对氟西汀诱导肝损伤减毒的临床前实验研究现状

Yilmaz 等[23]考察了咖啡酸苯乙酯(CAPE)对氟西汀诱导的大鼠肝毒性的保护作用,研究结果显示,给予雄性 SD 大鼠氟西汀(10 mg/kg)口服 7 d 引起了血清 ALT、AST 水平的显著升高及肝组织病变,还引起了血清和肝组织中总氧化剂状态(TOS)和氧化应激指数(OSI)的增加,以及总抗氧化能力(TAC)和对氧磷酶-1(PON-1)水平的降低,而联合 CAPE 腹腔注射干预可减轻氟西汀诱发的肝损伤。

Karimi-Khouzani 等[24]观察了没食子酸对氟西汀诱导的大鼠肝损伤的改善作用,研究结果显示,氟西汀(24 mg/kg)口服给药 1 个月引起了雄性 Wistar 大鼠显著肝损伤,其毒性机制涉及自由基和 TNF-α 有关的炎性反应;而联合没食子酸给药可显著改善氟西汀诱导的肝损伤。

Elgebaly 等[25]观察了橄榄油和橄榄叶 80% 乙醇提取物对氟西汀诱导的大鼠肝损伤的保护作用,研究结果显示,氟西汀(10 mg/kg)口服给药 7 d 引起了雄性大鼠显著肝损伤,其毒性机制涉及氧化应激、炎性反应和细胞凋亡,而联合橄榄油和橄榄叶 80% 乙醇提取物分别干预均可减轻氟西汀诱发的肝损伤。

Ganguly 等[26]研究联用黄芩苷(50、100 mg/kg)28 d 对氟西汀(10 mg/kg)口服给药诱导的 Wistar 大鼠肝损伤的保护作用及其初步的机制,结果表明,氟西汀诱导了大鼠肝损伤,而黄芩苷能够有效减轻氟西汀诱导的大鼠肝损伤,其减毒机制可能与抑制氧化应激和炎性反应有关。

Mohamed Kamel 等[27]观察了联用长春西汀(20 mg/kg)对氟西汀(10 mg/kg)口服给药诱导的大鼠肝损伤的保护作用及其初步的机制,研究结果表明,氟西汀诱导了大鼠肝损伤,而长春西汀能够改善氟西汀诱导的大鼠肝损伤,其减毒机制可能涉及氧化应激和炎性反应的抑制,以及过氧化物酶体增殖物激活受体 γ(PPAR-γ)表达的上调。

此外,Beigi 等[28]研究结果显示,鞣花酸和牛磺酸对氟西汀诱导的大鼠肝损伤具有保护作用,其初步的减毒机制与清除自由基和抑制炎性反应有关。

综上可知,氟西汀以 10 mg/kg 的剂量口服给予雄性 SD 大鼠 7 d 引起了肝损伤,CAPE、橄榄油和橄榄叶 80% 乙醇提取物干预均能够抑制氟西汀诱导的肝损伤,即对氟西汀诱导的肝损伤具有减毒作用;氟西汀以 10 mg/kg 剂量口服给药引起了大鼠肝损伤,而联用黄芩苷、长春西汀、鞣花酸或牛磺酸均能减轻氟西汀引起的肝损伤,其减毒机制涉及抑制氧化应激和炎性反应,或上调 PPAR-γ 的表达;氟西汀以 24 mg/kg 剂量口服给予雄性 Wistar 大鼠 1 个月诱发了显著的肝损伤,没食子酸干预能够抑制氟西汀诱导的肝损伤,即对氟西汀诱导的肝损伤具有减毒作用。然而,除 CAPE、黄芩苷、长春西汀、鞣花酸、牛磺酸、橄榄油、橄榄叶 80% 乙醇提取物、没食子酸之外,是否还有同样具有减毒作用甚或减毒效果更好的药物;深入的致毒及其减毒机制为何;为何对在雄性 Wistar 大鼠诱导的肝损伤比对在雄性 SD 大鼠诱导的肝损伤有更高的剂量以及更长的给药周期等,这些都是后续需要关注和澄清的问题。

2　氟西汀诱导肝损伤的研究策略

由以上研究现状可知,目前对抗抑郁药氟西汀诱导的肝损伤及其减毒作用已取得一定的研究进展,然而存在诸多问题,例如,氟西汀分别对小鼠和雌性大鼠是否同样会诱发肝损伤、是否存在性别差异、致毒机制为何、是否有减毒作用更好的药物特别是在中医药理论指导下更好的中药减毒措施及其机制等,均不清楚。针对抗抑郁药氟西汀诱导肝损伤的研究现状所存在的主要问题,后续研究至少有以下策略或举措:

(1)在小鼠上探索氟西汀诱导肝损伤的“量—时—毒”关系及其致毒机制。考察氟西汀引起肝损伤的最低剂量、最短时间,并与氟西汀临床常用剂量与抗抑郁治疗疗程进行比对,全面评估氟西汀的安全性,并为其安全用药提供针对性的应对预案或措施。

(2)探索氟西汀诱导肝损伤的性别差异及其机制。如果氟西汀诱导的肝损伤不存在性别差异,则至少从肝损伤的不良反应的角度来看,提示临床用药或无需考虑性别因素;同样,如果氟西汀诱导的肝损伤存在性别差异,若对雄性更敏感、毒性更强、中毒时间更早,则提示临床用药时或要注重性别的差异性,应对不同性别区别对待,反之亦然。

(3)探索对氟西汀诱导肝损伤更高效的减毒药物及其减毒机制,特别是中药对其的减毒及机制研究。后续研究可开展地黄(含其主要药效物质梓醇)等具有保肝[31-37]和抗抑郁[38-40]双重功能的特色中药对氟西汀诱导肝损伤的减毒增效作用及其机制的研究,拓展特色中药与氟西汀联合用药以提高氟西汀用药安全性和有效性。

3　结　语

尽管一线抗抑郁药物氟西汀在用药过程中可引起诸多不良反应[4-20],然而目前对其诱导的不良反应的临床前实验研究涉及面较窄。氟西汀诱导的不良反应的临床前实验研究主要集中在对氟西汀诱导的大鼠肝损伤及对其减毒研究方面,其中,致肝损伤模型的动物以雄性大鼠为主,给药途径以口服为主兼见腹腔注射,给药剂量主要在 8 ~ 24 mg/kg,给药周期主要在7 d ~ 1 个月不等,致毒机制涉及氧化应激、炎性反应、细胞凋亡等,已报道的减毒药物主要有没食子酸、CAPE、黄芩苷、长春西汀、鞣花酸、牛磺酸、橄榄油、橄榄叶 80% 乙醇提取物等,然而,对于小鼠和雌性大鼠是否同样能够诱发肝损伤、是否存在性别差异、深入的致毒机制及其分子靶点、是否还有其他同样具有减毒作用甚或减毒效果更好的药物等重要问题,迄今为止依然不清楚。因此,后续仍需加以关注和研究。本文为氟西汀诱导肝损伤的致毒机制及其减毒策略的深入研究提供文献支持和思路启发,助力氟西汀的安全用药进程。

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