

PCR 结果显示 LPS 腹腔注射 1 h 后,可导致 LTC₄s 的 mRNA 呈现一过性上调趋势,提示在炎症模型中海马中炎症分子前列腺素 E₂ 以及白三烯 C₄ 合成增加。**结论** 大鼠腹腔注射脂多糖 LPS 可引起学习与长期记忆能力损伤并致海马前列腺素 E₂ 以及白三烯 C₄ 合成增加。

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T15.7 基于系统毒理学的离子辐射的剂量反应关系

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摘要: **目的** 研究离子辐射剂量反应关系的种种可能性。**方法** 本研究利用系统毒理学的方法,建立细胞周期停滞模型,并与干扰模型与两步的癌症克隆增长模型相连接,模拟出了 J 型剂量反应曲线存在的可能性。具体方法是首先将模型模块化,分为系统模块、干扰模块以及病理模块。系统模块描述了细胞周期关卡控制传导途径。干扰模块描述了离子辐射引起的细胞周期关卡停滞。病理模块利用了两步的癌症克隆增长模型。各模块的数学模拟方式是利用系统动力学的方法,将传导途径中的各分子浓度变化建立微分方程组,并利用细胞周期是细胞分裂率的倒数而将系统模块/干扰模块与病理模块相连接,模拟出由不同剂量的离子辐射引起的癌症变异率。模型中的各参数依照已有的数学模型来定义,并用敏感性分析验证了模型参数的选取对于模拟结果影响不大。**结果** 此方法模拟出了直线型以及 J 型剂量反应关系的存在。**结论** J 型剂量反应关系存在的内在原因是由离子辐射引起的细胞周期关卡停滞时间随着离子辐射剂量的增加而趋于饱和。

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T16 毒物代谢与毒代动力学

T16.1 基于毒物转运转化性质的毒理学评价和机制

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摘要: 毒物对于机体而言是外源性物质,进入体内后经被动转运或经摄取或外排转运体介导转运,吸收入血、分布至靶器官或排泄器官,发挥毒理效应或者加速排出体外;在代谢酶的作用下经历生物转化,生成活化产物或无毒产物。毒物的体内转运转化过程直接影响其吸收、分布、代谢和排泄过程,进而导致毒物的增毒或减毒。因此,毒物的转运转化研究是理解其中毒机制和解毒过程的必要前提,通过调控毒物基于转运体和代谢酶的体内处置过程,可以达到减毒或抗毒的目的。体外试验体系是研究毒物基于转运转化的毒理学机制的首选方法,具有通量高、易控制、重复性好、可分别考察多个因素的影响及机制、以及可应用人源性材料、便于进行种属之间的比较等优点。应用肝 S9、肝微粒体等亚细胞成分或人重组 I 相和 II 相酶,以及在体肝肠灌流模型,可以评价代谢酶对毒物的代谢转化作用;应用单层细胞转运模型或脑内皮细胞和胶质细胞的共培养模型,可以评价毒物的血脑屏障通透性及中枢分布与毒性的关系;应用原代培养肝细胞,可以评价毒物肝摄取、代谢、胆汁外排及肝毒性。本报道介绍了基于转运转化的毒物减毒或增毒作用,以及相关的机制研究。例如,在体外代谢转化试验体系中,研究了硫代磷酸酯农药经细胞色素 P450 酶氧化脱硫或酯酶水解

的活化增毒及减毒过程,以及代谢转化的种属差异。硫代磷酸酯农药在大鼠肝微粒体主要以氧化脱硫、生成毒性更高的活化产物为主;在人肝微粒体中则以酯酶代谢、生成无毒的水解产物为主。由此预测,其在人体的毒性可能低于大鼠。应用体外单层细胞转运模型和体内稳态分布模型,研究了外排转运体介导的强效麻醉性镇痛药跨血脑屏障通透性,以及转运体调控与其毒副作用的相关性。研究发现,这类药物是外排转运体的底物,与转运体抑制剂合用能显著改变药物的血脑屏障通透性,成倍提高其脑组织分布水平,引起显著的呼吸抑制毒性。应用原代培养的大鼠肝细胞模型,评价了转运体介导的雷公藤甲素肝摄取和胆汁排泄,以及肝代谢酶介导的代谢转化,研究了转运转化调控与其毒性的关系。研究确定雷公藤甲素是代谢酶和转运体的双重底物,肝代谢酶或转运体的抑制和诱导均能引起雷公藤甲素肝细胞浓度的变化,使肝毒性增大或降低。由此提示,当雷公藤甲素与其他临床药物合用时,存在药-药相互作用的益处或风险。

关键词: 代谢; 转运; 细胞色素 P450 酶; 转运体; 毒性作用

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T16.2 Toxicokinetic behavior assessment prediction of the ADME Properties of alkylated naphthalenes by consideration of relevant physicochemical and dystemic toxicity data: Proof of concept

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Abstract: In some cases, it may be possible to predict the toxicokinetic behavior (ADME) of a substance by considering its physicochemical properties as well as relevant toxicity data, such as data from a series of structurally related chemical analogs. This is the approach supported by the European Union's REACH regulation. The present case study aims to validate the toxicokinetic behavior assessment approach via comparison of the predicted ADME properties of a substance to the experimentally-determined ADME properties from robust toxicokinetic (TK) studies with the radiolabelled substance. This case study was conducted with an alkylated naphthalene (AN) compound, AN-600, where 600 denotes a molecular weight (MW) of 600 g·mol⁻¹. Based on its physicochemical properties, including molecular weight, water solubility and octanol/water partition coefficient (LogKow), AN-600 is predicted to have inherently low systemic bioavailability. This prediction was consistent with existing results of several toxicity studies in which there was no evidence of systemic absorption or toxicity. It was also predicted that among AN structural analogs differing in alkyl chain length and molecular weight, there would be an inverse relationship between molecular weight and bioavailability, consistent with pharmacologic principles. This inverse relationship prediction was supported by TK data from AN analogs, specifically AN-212 (MW = 212) and AN-379 (MW = 379) which had 85% and 10% oral bioavailability, respectively. Furthermore, there were observed trends of decreasing systemic absorption in repeat-dose dermal studies of AN-600 analogs with increasing molecular weight and there was no evidence of absorption found in a dermal study with AN-600 itself. Finally, available basic TK data for analogs suggested that any absorbed material would be metabolized by side chain oxidation of the alkyl group, producing sulfate and glucuronide metabolites which would be ultimately excreted in the urine. In total, the above evidence led to a prediction that very little AN-600 could be absorbed by the oral or dermal routes. Exposure by inhalation is not expected due to the high molecular weight and low vapor pressure of AN-600. Subsequent to this prediction, extensive repeated dose, reproductive toxicity and toxicokinetic studies, were carried out on AN-600. In the toxicokinetics studies, systemic oral and dermal absorption was ≤1.3% and ≤0.16%, respectively, and the material that was absorbed had a half-life of 13–24 h, with the remainder of the oral dose quantitatively recovered unabsorbed in the feces after 120 h. The dermal dose was recovered quantitatively unabsorbed at the skin application site. These findings confirmed the prediction that the bioavailability of AN-600 is extremely low; consistent with the prediction that it would not exert systemic toxicity. The predicted lack of toxicity was confirmed through 90-d dermal and two-generation reproductive toxicity studies in