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论著

去甲阿佐昔芬与谷胱甘肽的结合及其对谷胱甘肽转移酶的抑制作用

余波澜，郭小桥，司沙沙

广州医学院第三附属医院妇产科研究所，广东 广州 510150

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摘要 目的 探讨阿佐昔芬代谢产物去甲阿佐昔芬与谷胱甘肽及谷胱甘肽转移酶的相互作用。方法 SD大鼠ip注射去甲阿佐昔芬10 mg·kg^{-1}溶液，每天1次，连续3 d，第4天处死大鼠，提取肝内去甲阿佐昔芬与谷胱甘肽结合产物，利用高效液相色谱-质谱分析比较和鉴定去甲阿佐昔芬在肝微粒体和大鼠肝内的谷胱甘肽结合产物。雷洛昔芬20 μmol·L^{-1}，4-羟基他莫昔芬20 μmol·L^{-1}和去甲阿佐昔芬20 μmol·L^{-1}分别加入大鼠肝微粒体系中孵育30 min后，应用试剂盒测定谷胱甘肽转移酶活性，考察其对谷胱甘肽转移酶的体外抑制作用，并测定了去甲阿佐昔芬0，5，10，20和30 μmol·L^{-1}对谷胱甘肽转移酶的抑制强度。结果 体内实验表明，去甲阿佐昔芬代谢产物可在大鼠肝中形成谷胱甘肽结合物。质谱分析鉴定其主要成分为去甲阿佐昔芬双醌甲基化合物与谷胱甘肽的单价结合物。体外的酶活性测定表明，去甲阿佐昔芬能浓度依赖地抑制谷胱甘肽转移酶活性，去甲阿佐昔芬20 μmol·L^{-1}可以抑制谷胱甘肽转移酶90%以上的活性。与雷洛昔芬和4-羟基他莫昔芬相比，去甲阿佐昔芬是最强的抑制剂，在相同浓度下，其抑制率显著高于雷洛昔芬和4-羟基他莫昔芬(P<0.01)。结论 阿佐昔芬的代谢产物具有较强的反应性，可能会与生物分子中的巯基发生共价结合。其在临床上的长期生物学效应值得进一步探讨。

关键词 阿佐昔芬 去甲阿佐昔芬 醌类 谷胱甘肽转移酶 抑制作用

分类号 R984

Adduction of desmethylarzoxifene with glutathione and their inhibitory effect on glutathione S-transferase

YU Bo-lan, GUO Xiao-qiao, SI Sha-sha

Institute of Gynecology and Obstetrics, the Third Affiliated Hospital, Guangzhou Medical College, Guangzhou 510150, China

Abstract

OBJECTIVE To investigate the interaction of active metabolite desmethylarzoxifene (DMA) of arzoxifene with glutathione (GSH) and glutathione *S*-transferase (GST). **METHODS** SD rats were ip given DMA 10 mg·kg^{-1}, once daily, for 3 d and sacrificed on the 4th day. The DMA-GSH adducts were isolated from their livers, and identified and compared with DMA-GSH adducts in rat liver microsomal incubations using LC-MS. GST activity assays were performed and the inhibitory effects on GST *in vitro* by raloxifene, 4-OH tamoxifen, and DMA were compared. In addition, the inhibitory rates of different concentrations of DMA were assayed and the IC_{50} was calculated accordingly. **RESULTS** *In vivo* experiments showed that DMA diquinoid metabolites could form GSH adducts in rat livers. LC-MS analysis identified an abundant isomer of DMA di-quinone methide and GSH adducts, as a double charged ion $^{2+}$ at *m/z* 384. GST enzyme activity assays indicated that DMA inhibited GST activity in a concentration-dependent manner, and about DMA 20 μmol·L^{-1} could inhibit GST activity by over 90%. Compared to raloxifene and tamoxifen, DMA was the strongest inhibitor for GST, with a significant higher inhibitory rate than that of raloxifene and tamoxifen (P<0.01). **CONCLUSION** DMA can react with the thiols of biomolecules *in vivo* and *in vitro*, which suggested the potential biological effects of arzoxifene in clinic usage.

Key words arzoxifene desmethylarzoxifene quinones glutathione transferase inhibitory action

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通讯作者 余波澜,E-mail:yubolan@gmail.com,Tel:(020)81292202 yubolan@gmail.com

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