

北美黄连碱对细粒棘球蚴超微结构的影响

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Acta Pharmacologica Sinica 1989 Mar; 10(2): 185-187Effect of *d*-hydrastine on the ultrastructure of experimental *Echinococcus granulosus* cyst in miceYE Yu-Cong, CHEN Qin-Ming, HAI Ping, CHAI Feng-Ling, ZHOU Sheng-Xiang
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Abstract The ultrastructural changes in the germinal membranes of *Echinococcus granulosus* cysts treated with *d*-hydrastine (3.75 mg/(kg·d), ig) for 20 d were studied. Cysts from *d*-hydrastine treated mice were shown by transmission electron microscope to have dissolution of the microtriches, disturbance of organelles in their arrangement, dilatation and disruption of microtubules, increase in size and number of lysosomes, a decrease in number of Golgi complexes and lessening in density and swelling of mitochondria. Under scanning electron microscope, many pits arising from the outer and inner surfaces of the germinal membrane were observed. It seems that *d*-hydrastine has a profound intracellular effect on experimental *Echinococcus granulosus* cysts in mice, and that it may be a promising drug for treating hydatidosis.

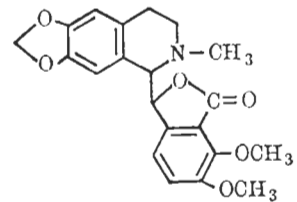
Key words *d*-hydrastine; *Echinococcus granulosus*; electron microscopy; scanning electron microscopy

提要 感染细粒棘球绦虫原头节 100 d 后的小鼠, 经北美黄连碱治疗后, 其体内棘球蚴生发膜的皮层微毛消失, 细胞器排列紊乱, 胞浆中微管局限性扩张破裂, 高尔基复合体减少, 线粒体肿胀, 生发膜的角质层面和囊腔面出现许多陷窝样损害。提示该药对细粒棘球蚴有广泛的细胞内效应。

关键词 *d*-北美黄连碱; 细粒棘球蚴; 电子显微镜检查; 扫描电子显微镜检查

棘球蚴病(包虫病, echinococcosis)是人畜共患的寄生虫病, 危害严重, 对该病的化学治疗至今尚无理想的药物。苯并咪唑类⁽¹⁻²⁾、吡喹酮⁽³⁾等的疗效均不够令人满意。

通过体外培养⁽⁴⁾、动物实验⁽⁵⁾与临床观察⁽⁶⁾, 观察到某些紫堇属植物对包虫病有一定疗效。本文系首次报道右旋北美黄连碱(*d*-hydrastine)⁽⁷⁾对细粒棘球蚴超微结构的影响。

*d*-Hydrastine**Materials and methods**

右旋北美黄连碱系从直茎紫堇 (*Corydalis stricta* Steph) 中提取分离所得到的白色单体结晶, 由中国医学科学院药物研究所植物化学研究室供给, 先用 1% HCl 溶解, 然后用稀碱溶液调 pH 至 5 再用蒸馏水配制成含有 0.0375% 北美黄连碱溶液。

瑞士种小鼠体重 $27.0 \pm SD 2.1$ g, ♀, 每鼠腹腔感染事先经无菌方法处理的绵羊肝细粒

棘球绦虫原头节 2000 个。将 20 只感染 100 d 的小鼠随机分为两组。对照组 ig 自来水, 实验组 ig 北美黄连碱溶液。根据小鼠对该药的最大耐受量, 确定剂量为 $3.75 \text{ mg}/(\text{kg}\cdot\text{d}) \times 20$, 停药后观察 30 d。于给药后 50 d 拉颈处死小鼠, 取出棘球蚴囊称重, 并计算其减轻率。减轻率 = $(\text{对照组平均棘球蚴囊重量} - \text{实验组平均棘球蚴囊重量}) / \text{对照组平均棘球蚴囊重量} \times 100\%$ 。从每只小鼠取部份棘球蚴囊作病理检查, 其余作腹腔重移植。3 个月后解剖小鼠, 观察其体内棘球蚴囊的转归。

扫描电镜 (CamScan 3-30ACV) 与透射电镜 (H-600) 标本的制备: 取每只小鼠的棘球蚴囊 $2 \times 4 \text{ mm}$ 组织块各 2 个, 制作电镜标本⁽⁶⁾。

Results

病理组织学观察 感染后 150 d 的 10 只对照组小鼠, 每鼠平均棘球蚴囊湿重为 $550 \pm 120 \text{ mg}$, 右旋北美黄连碱治疗组 10 鼠为 $107 \pm 24 \text{ mg}$, 棘球蚴囊减轻率为 80.5%, 相差非常显著 ($P < 0.001$)。病理切片显示对照组棘球蚴生发膜发育良好, 角质层的板层状结构整齐且较厚。治疗组的棘球蚴囊壁很薄, 板层状条纹断裂并有空泡形成, 生发层细胞胞浆内出现空泡样变性。将棘球蚴囊移植后, 对照组 10 只小鼠的棘球蚴全部生长发育, 治疗组 10 只小鼠中有 7 鼠体内的棘球蚴均呈现变性和坏死。

扫描电镜观察 对照组棘球蚴生发膜的角质层面有高低不平的丘状隆起或外生性育囊 (育囊外部发育现象), 其表面可见长短不等的微毛 (Fig 1-A 见 Plate 1, 以下各图同); 生发膜的囊腔面呈现柱状, 丘状突起与深浅不一的凹陷, 表面有许多球形与鹅卵石样的突起, 系内生性育囊 (Fig 1-B)。治疗组生发膜角质层面的微毛断裂脱落, 有许多大小不等, 深浅不一, 边缘不整齐的陷窝形成 (Fig 1-C); 生发膜囊腔面的乳头状或柱状突起排列紊乱, 未见内生性育囊, 但可见许多不规则的细胞碎片 (Fig 1-D)。

透射电镜观察 对照组棘球蚴的角质层由细丝和小泡构成。生发膜含皮层细胞, 肌细胞, 焰细胞, 导管细胞等。生发膜皮层与角质层邻接, 由皮层细胞的远端胞浆和微毛构成合胞体区带, 微毛数量多且发育良好。皮层细胞区为生发膜第二区带, 皮层细胞一般有一个胞核, 核内可见电子密度大, 大小不等的颗粒状异染色质与着色浅且均匀细密的常染色质, 核膜为双层, 在核周胞浆中可见丰富的微管, 线粒体, 高尔基复合体, 溶酶体, 光面与粗面内质网, 囊泡及核糖体等 (Fig 1-E, F)。治疗组的棘球蚴生发膜示有微毛发育不良, 脱落或消失; 皮层细胞胞浆内可见许多空泡, 原来的微毛与微管已难见到; 线粒体排列紊乱, 内外膜肿胀, 嵴变形或断裂消失, 基质明显减少, 电子密度降低, 局部出现空泡; 高尔基复合体解体为小泡散布于胞浆中; 溶酶体数量增多; 胞核核周间隙扩大 (Fig 1 G-I)。

Discussion

已知不同部位的生发膜存在着代谢高度差异的区域, 在形成育囊与原头节的部位还有脂质和多种酶的积聚⁽⁸⁾, 表明这些物质对原头节、育囊的生长至关重要。经北美黄连碱治疗后, 生发膜的角质层面和囊腔面未见有育囊生长, 仅观察到角质层面有许多大小不等的陷窝, 囊腔面的乳头状突起排列紊乱、断裂; 皮层细胞远端胞浆与微毛发育不良, 远端胞浆内空泡增多。Lascano⁽⁹⁾ 等认为生发膜皮层区是大分子物质渗透到棘球蚴内的唯一物理屏障, 因而随着皮层区发育受阻与微毛的消失, 使生发膜对大分子物质渗透的栅栏作用受到影响。另外, 皮层细胞的分泌物与角质层的形成有关, 而后者又起到保护生发膜作用, 使虫体免遭宿主的攻击, 并控制着营养物质的输送; 皮层细胞合成的水解酶经微管系统转运到角质层, 可起到营养物质的外消化作用, 当胞浆微管系统遭受破坏时, 引起水解酶在合成部位长时间的堆积, 并导致细胞的自溶, 推想棘球蚴

表面陷窝形成可能与此机理有关。

用北美黄连碱治疗包虫病尚未见文献报道。本文的实验结果表明尽管该药的总剂量仅为紫堇总生物碱的 1/50，但棘球蚴囊的减轻率却较后者(67%)⁽¹⁰⁾ 为高，表明右旋北美黄连碱很可能系抗包虫的有效成分之一。

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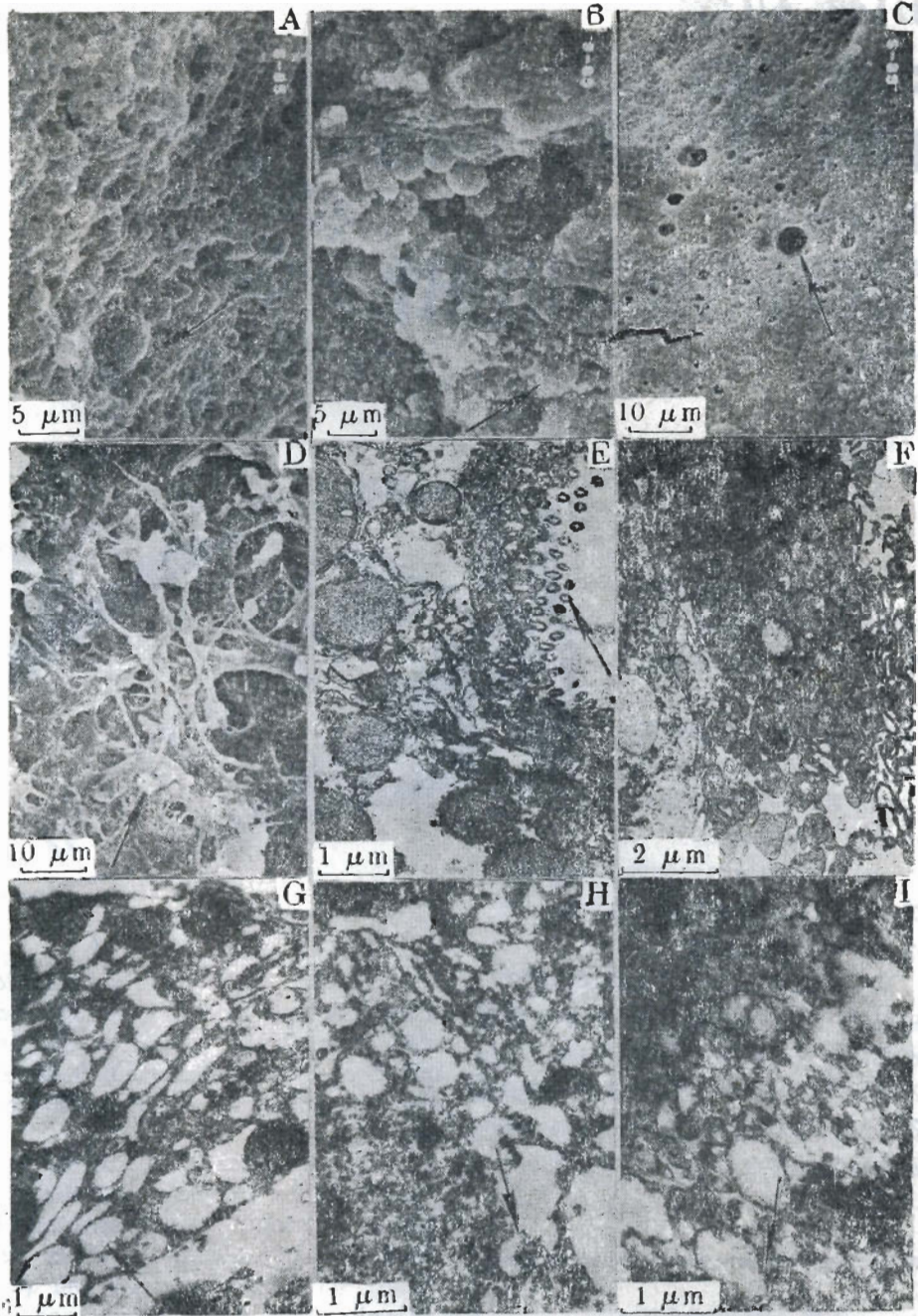


Fig 1. Effect of *d*-hydrastine (3.75 mg/(kg·d)×20, ig) on the ultrastructure of experimental *Echinococcus granulosus* cyst. A)–D) Scanning electron microscope. A) B) Untreated mice and C) D) treated mice. A) Normal appearance of the outer surface of germinal membrane, showing brood capsule (arrow), ×2000. B) Normal appearance of the inner surface of germinal membrane, showing protrusion and the brood capsule (arrow), ×1500. C) The irregular outer surface of germinal membrane and the numerous pits (arrow), ×1000. D) The disorder inner surface of germinal membrane, dropped cell debris (arrow), ×1000. E)–I) Transmission electron microscope. E) F) Untreated mice and G) H) I) treated mice. E) The normal appearance of the distal cytoplasm and microtriches of the tegumental cell, ×12 000. F) The normal tegumental cell, ×8000. G) A large number of vesicles (arrow) of the distal cytoplasm and dissolution of the microtriches, ×10 000. H) Most of the microtubules focally dilated and ruptured (arrow), ×15 000. I) Swelling and vacuolar degeneration of mitochondria in tegumental cell (arrow), ×17 000. (See p 186)