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降钙素的中枢性镇痛作用及与中枢单胺类递质的关系

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Central analgesic action of calcitonin and its relationship with central monoamine transmitters

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ABSTRACT The analgesic action of calcitonin (0.25 MRC units · kg^{-1}) injected into lateral cerebroventricle was investigated in rats. The pain threshold was evaluated by the tail—flick test. The influences of icv naloxone 5 μg/rat, a blocker of opiate receptor, on the analgesic action of calcitonin were observed. The results showed that icv calcitonin produced a significant analgesic action, which was reversed by naloxone. While the pain threshold was raised by calcitonin, the contents of central monoamines (5—HT, NE, DA) in brain (diencephalon, brain stem) were examined by fluorophotometry, which were increased remarkablly. It is suggested that calcitonin—induced analgesia is related to the opiate receptors and the contents of 5—HT, NE, and DA in CNS.

KEY WORDS calcitonin; naloxone; analgesia; brain

提要 用辐射热—甩尾法测定大鼠痛阈, 观察 calcitonin 注入侧脑室引起的痛阈变化. 结果表明, calcitonin 具有显著镇痛作用, 此镇痛作用可被侧脑室注射 naloxone 翻转. 在 calcitonin 引起痛阈升高时, 用荧光分光光度法测得脑组织(间脑和脑干)的单胺类递质(NE, DA, 5—HT)含量明显升高. Calcitonin 的镇痛作用与脑内阿片受体及单胺类递质的含量有关.

关键词 降钙素; 纳洛酮; 镇痛; 脑

大鼠及兔侧脑室注入 calcitonin 均引起痛阈升高[1,2], 但 calcitonin 的中枢性镇痛作用是

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通过何种途径产生以及与阿片受体及有关神经递质的关系如何目前尚无一致看法[2-4]. 本文探讨了 calcitonin 的中枢镇痛作用与阿片受体的关系，并测定了 calcitonin 引起痛阈升高时间脑和脑干 5-羟色胺(5-HT)去甲肾上腺素(NE)和多巴胺(DA)的含量变化.

METHODS

Wistar 大鼠 70 只，♀♂不限，体重 211 ± *s* 18 g，随机分为对照组，calcitonin 组，naloxone 组，合并给予 calcitonin 和 naloxone 组. ip 水合氯醛 400 mg · kg^{-1} 麻醉下暴露颅骨，在立体定位仪上参照 Koning 和 Klippele 图谱于单侧侧脑室埋植外径 0.7 mm，内径 0.4 mm 的不锈钢套管，并以牙科用磷酸锌固定，术后 5 d 开始实验.

测痛在安定的环境中进行，室温为 20 ± 0.5℃，用辐射热-甩尾法测定痛阈，以辐射热引起的甩尾反应潜伏期作为痛阈指标，调解辐射热强度，使基础痛阈控制在 4-5 s 之间，以给药前 3 次测定的均值为基础痛阈.

用恒速微量注射器将药物匀速(1 μl · min^{-1})注入侧脑室，注药后每 5 min 测痛一次，观测 1 h，结果用甩尾反应潜伏期实测值(s)表示.

于侧脑室注药 15 min 时迅速将大鼠断头取脑，在冰盘上分离出间脑和脑干，称重后迅速置冰水中匀浆，取上清液经提取[5]后，用荧光分光光度计(Hitachi F-3000)检测脑组织 5-HT，NE，DA 的含量.

RESULTS

Pain threshold 对照组大鼠 icv 生理盐水(saline)不影响痛阈；大鼠 icv calcitonin 注射液(日本东洋酿造株式会社产)0.25 MRC units · kg^{-1}，5 min 后痛阈较对照组显著升高($P<0.05$)，20 min 左右达最大值，其后逐渐下降，60 min 左右基本恢复到基础痛阈；大鼠 icv naloxone (Sigma 产) 5 μg / rat 后，观察 60 min，各时间较对照组均无显著差异；icv naloxone 5 μg / rat 后 15 min，再 icv calcitonin 0.25 MRC units · kg^{-1}，观察 60 min，各时间较对照组均无显著差异(Fig 1).

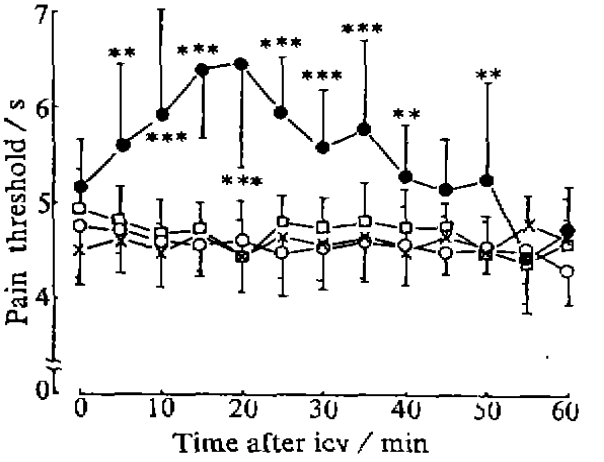

Fig 1. Effects of icv saline (○), calcitonin (●, 0.25 MRC units · kg^{-1}), naloxone (×, 5 μg · rat^{-1}), and naloxone + calcitonin (□) on pain threshold in rat tail-flick test. $n=10$, $\bar{x} \pm s$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* saline.

Monoamines in brain 大鼠 icv calcitonin 15 min 时，痛阈升至最大值，此时大鼠间脑和脑干内 NE，DA 和 5-HT 的含量均较对照组明显升高；在注射 calcitonin 前预先注射 naloxone 组大鼠间脑和脑干内 NE，DA 和 5-HT 的含量均与对照组无显著差异(Fig 2).

DISCUSSION

本实验结果表明，向大鼠侧脑室注入 calcitonin 可产生明显的全身镇痛作用；这与其他实验室的报道结果相一致[2-4]. 这种镇痛作用可被由脑室内注入阿片受体拮抗剂 naloxone 所阻断. 提示 calcitonin 的镇痛作用与阿片受体有关. 有的作者从兔皮下注入 naloxone，不能阻断由脑室内注入 calcitonin 所产生的镇痛作用，因而认为脑内阿片受体不

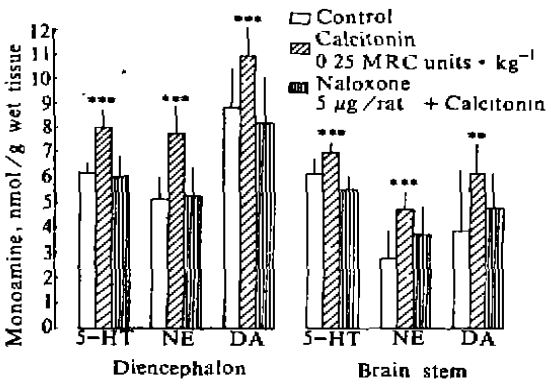

Fig 2. Monoamine concentrations in brain 15 min after icv drugs in rats. $n=10$, $\bar{x} \pm s$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **control.**

参与 calcitonin 的镇痛作用[2]，可能与其注入 naloxone 的途径不同，动物的种属差异以及 naloxone 的剂量不足所致.

已知中枢 5-羟色胺能和去甲肾上腺素能系统在中枢性痛觉整合过程中起着很重要的作用. 利血平能拮抗大鼠 calcitonin 的镇痛作用，5,7-双羟色胺(5,7-DHT)注入中缝背核损毁神经元，calcitonin 的镇痛作用也消失[6]，提示中枢 5-HT 能途径可能与 calcitonin 的镇痛作用有关. Guidobono 等[7] 在大鼠 icv calcitonin 前预先注射 6-羟多巴胺选择性地损毁儿茶酚胺能神经元，结果发现 calcitonin 的镇痛作用明显减弱，同时给 α 和 β 受体阻断剂也表现出有明显的对抗 calcitonin 引起的镇痛作用. 大鼠 icv 5,7-DHT，使中枢 NE 含量明显降低，也导致 calcitonin 作用的消失[4]. 由此推测中枢儿茶酚胺能途径可能与 calcitonin 的镇痛作用有关. 也有人认为中枢单胺类递质中只有 5-HT 与 calcitonin 的镇痛作用有关[3]. 本实验室是在 calcitonin 引起痛阈升高时检测不同脑区单胺类神经递质的含量，能更直接地反映单胺类递质与 calcitonin 镇痛效应之间的关系. 因而证明：calcitonin 引起痛阈升高时脑组织 5-羟色胺，去甲肾上腺素，多巴胺的含量均增加，说明中枢单胺类递质的含量与 calcitonin 的镇痛作用有关.

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