0.15 mg·kg^{-1}还可使老年小鼠的 SDL 各延长 187 %，209 %和 152 %，EL 各缩短 52 %，62 %和 57 %. 三药尚明显改善由环己酰亚胺或东莨菪碱产生的记忆保持损害. N-CS 无上述作用. 结论：Sub 和 Sub-DU 对记忆的改善作用与其抗 AChE 有关.

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Effects of calcitonin injected into various brain areas on pain threshold and Ca^{2+} in rats

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KEY WORDS pain threshold; calcitonin; cerebral ventricles; periaqueductal gray; calcium

AIM: To study the effects of calcitonin (Cal) injected into different brain areas on pain threshold. **METHODS**: The analgesic effects of Cal were investigated in rats by the tail-flick test. **RESULTS**: Cal injected into lateral cerebral ventricle (LCV) or periaqueductal gray (PAG) increased obviously the pain threshold to 49 ± 22 % or to 68 ± 12 % ($P < 0.01$), respectively. When PAG was blocked with lidocaine, the analgesic effect of Cal injected into LCV was lowered 41 ± 9 %. Cal injected into habenula (Hab) decreased the pain threshold to − 30 ± 5 % ($P < 0.01$). **CONCLUSION**: Cal in different rat brain areas induced different effects on pain responses: analgesia or hyperalgesia, and showed that PAG played an important role in the analgesic effect induced by Cal, and the changing of pain threshold was mediated by the Ca^{2+} in brain.

Calcitonin (Cal) showed an analgesic action which is involved in the binding of opioid receptors in brain[1]. Periaqueductal gray (PAG) and Habenula (Hab) are the key relays in the realizing of the analgesic action of morphine and acupuncture[2,3]. The Ca^{2+} in CNS antagonizes the analgesic actions of both morphine and acupuncture[4,5]. What is about the role of Cal and what is the relationship between Cal analgesia and Ca^{2+}? To assay this problem will benifit the comprehension of the mechanism of Cal analgesia.

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METHODS

Wistar rats of either sex ($n = 76$) weighing 220 ± 30 g were anesthetized with chloral hydrate 0.4 g·kg^{-1}. Stainless steel guide cannula (OD 0.7 mm, ID 0.4 mm) were inserted into unilateral ventricle, bilateral of PAG, and Hab according to the atlas of Konig & Klippel and the cannula were anchored with dental cement to the skull. A stainless steel cannula (OD 0.4 mm) was in the guide cannula for injection of drugs. After 5 d, experiments were carried out in a quiet room at 20.0 ± 0.5 ℃. The pain threshold were measured by the tail-flick test with a radiant heat sustained for 4 - 5 s. The basal pain threshold was the average of 3 trials before the drug was used.

Cal was injected into LCV 1 μL·min^{-1}, 5 μL; bilateral PAG 1 μL·min^{-1}, 2 μL/side; bilateral Hb 0.25 μL·min^{-1}, 0.5 μL/side.

Injection sites were marked by injecting 2 % pontamine sky blue. The brains were stored in 10 % formalin for at least 5 d. Cannula tip placements were verified from 40 μm coronal sections. Rats were included if the target areas were correct.

The Cal was from Tou You Corporation, Japan, 10 kU·L^{-1} injection. Other drugs were dissolved in saline.

RESULTS

1 Analgesic effect of Cal injected into LCV, PAG and Hab Five minutes after Cal injected into LCV 12.5 - 50 μU in 5 μL the pain threshold was raised, reached the maximum at 20 min, and recovered to the basal level after 1 h. The analgesic

actions of these doses showed dose-dependent during 10-15 min ($P<0.05$) (Fig 1A).

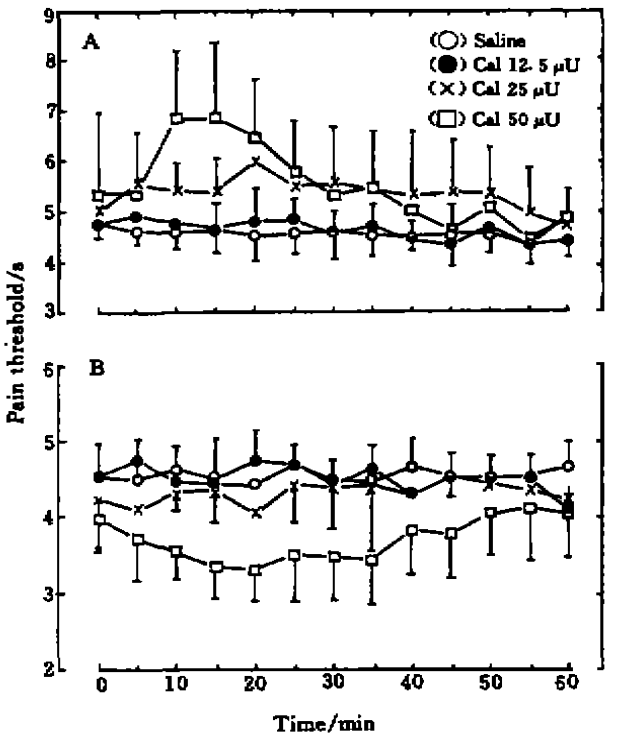

Fig 1. Effects of Cal injected into LCV (A, $n = 24$) and into Habenula (B, $n = 13$). $\bar{x} \pm s$.

Cal 400 μU in 2 μL were injected into both sides of PAG, the pain threshold were raised immediately and reached the maximum at about 20 min ($P < 0.05$). Compared with LCV, the analgesic effect in PAG was greater ($P < 0.05$). When the pain threshold was raised 10 min after Cal injected into LCV, 2 % lidocaine 2.0 μL injected into PAG restored immediately the pain threshold almost to the basal level. Instead of lidocaine, saline into PAG had no effect on the pain threshold (Fig 2A).

When bilateral Hab were injected Cal 400 μU in 2.5 μL, the pain threshold was lowered to nadir at 20 min, and recovered at 55 min. But the smaller doses Cal 250 μU or 125 μU in 2.5 μL yielded no changes on the pain threshold.

Saline injected into the above areas did not changed the basal level (Fig 1B).

2 Effect of Ca^{2+} on Cal-caused analgesia

When the pain threshold was raised 10 min after Cal injection, $CaCl_2$ 50 nmol · L^{-1} 5 μL injected into LCV recovered the pain threshold to the basal level immediately. However, after saline injection, $CaCl_2$ did not change the basal pain threshold (Fig 2B).

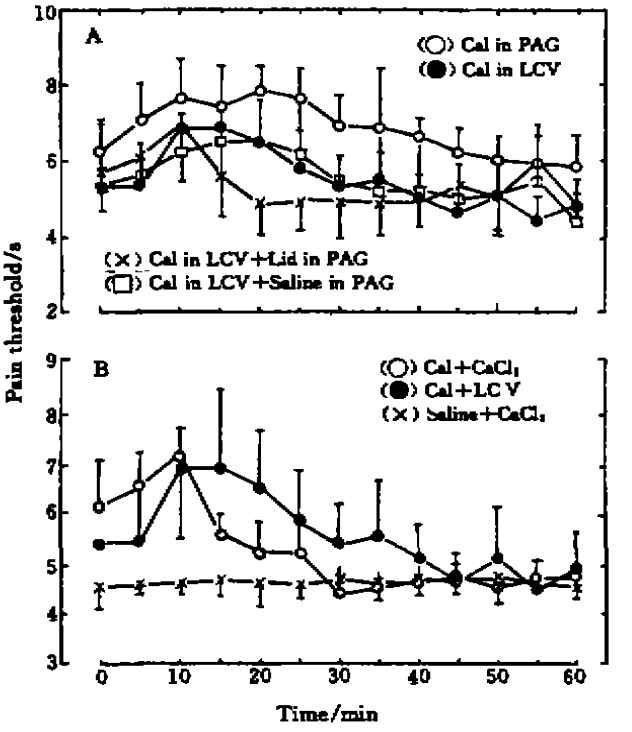

Fig 2. Effects of PAG (A, $n = 15$) and $CaCl_2$ (B) on Cal-induced analgesia. $\bar{x} \pm s$. (B) $n = 10$ in (○) Cal + $CaCl_2$, $n = 8$ in (●) Cal + LCV, and $n = 9$ in (×) saline + $CaCl_2$.

DISCUSSION

The results that Cal injected into LCV and PAG produced analgesia were consistent with the findings reported by our lab[6] and other labs[1,7]. It was found that the analgesic effect of PAG was stronger than that of LCV. PAG is the concentrate area of Cal binding sites in CNS[8]. Therefore, it is clear that Cal injected into PAG can produce a powerful analgesia, and that the central analgesia of Cal is realized by PAG which is the central link of limbic midbrain circuit.

Up to now, no news about Cal receptors in Hab is reported. The relation between analgesic of Cal and Hab is also entitlely unknown. In this study Cal injection into Hab produced hyperalgesia.

It might be either the result of Cal exciting on Hab which was similar to the condition of *L*-glutamate exciting on Hab[2], or the result of changing Ca^{2+} concentration which might promote ACh release from Hab to excite neurons of Hab[9].

A number of investigators reviewed that Ca^{2+} can antagonize the analgesic effect of morphine and acupuncture[10,11]. In this study the results showed that the analgesic effect of Cal was antagonized by Ca^{2+}. So, the changes of Ca^{2+} in brain could influence obviously the analgesic effect of Cal.

In brief, Cal injection into various areas in CNS might induce different effects: analgesia or hyperalgesia, which have something to do with the Ca^{2+} concentration in brain. PAG could possess a vital role in the analgesic action of Cal.

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218-220

大鼠脑内不同部位注射降钙素对痛阈及 Ca^{2+} 的影响

R964

R971.1

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关键词 痛阈；降钙素；脑室；中脑导水管周围灰质；钙

A **目的**：观察降钙素对大鼠不同脑区痛阈的影响. **方法**：向大鼠不同脑区注射降钙素(calcitonin, Cal)，以辐射热甩尾阈值为指标测定痛阈变化. **结果**：Cal 侧脑室(VLC)注射引起痛阈明显升高；同时发现向中脑导水管周围灰质(periaquaductal grey, PAG)注射 Cal，痛阈升高幅度更大，表明 PAG 在 Cal 的中枢镇痛效应中起重要作用. 而向缰核(habenula, Hab)注射 Cal，痛阈降低. Cal 对痛阈的影响与脑内 Ca^{2+} 有关