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关键词 四氢原小檗碱类；Sch-23390；螺哌隆；鸟苷三磷酸；纹状体；多巴胺 D_1 受体；多巴胺 D_2 受体；放射配位体测定；千金藤立定；12-氯代斯阔任

目的：研究四氢原小檗碱类(THPB)对脑内多巴胺受体 D_1 和 D_2 亚型的结合特性，并阐明它们之间的构效关系. 方法：放射配位体测定结合双位点模型分析. 结果：4 个 THPB 与 D_1 受体以 R_H 和 R_L 双位点结合，它们在 C_2 和 C_9 或 C_2 和 C_{10} 位有两个羟基，另外 11 个 THPB 与 D_1 受体以单位点结合. 对于 D_2 受体，11 个被检测的化合物均以单位点结合，其中，在 C_2 位有羟基的 THPB 亲和力最强. 结论：在 C_2 和 C_9 或 C_2 和 C_{10} 位有双羟基的 THPB 具有 D_1 受体激动剂的内在活性，其它 THPB 则无此活性. 11 个 THPB 均为 D_2 受体拮抗剂.

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Carbamazepine facilitates effects of GABA on rat hippocampus slices

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KEY WORDS carbamazepine; GABA; baclofen; hippocampus; evokedpotentials

AIM: To study the influence of carbamazepine (Car) on GABA effect in hippocampus. **METHODS**: Evoked potentials were recorded on pyramidal cells in CA1 after stimulation (0.5 Hz, 50 μs) to Schaffer collaterals in rat hippocampal slices (350 μm). **RESULTS**: Car 0.1 and 0.2 mmol·L^{-1} did not affect field potentials, whereas Car 0.2 mmol·L^{-1} plus GABA (0.1 － 1 mmol·L^{-1}) gave rise to a stronger inhibition on field potentials than that of GABA alone. Bicuculline did not reverse Car facilitation on GABA inhibition on field potentials. (－)-Baclofen was more effective in inhibiting field potentials than GABA. Car 0.2 mmol·L^{-1} plus (－)-baclofen (1 － 5 μmol·L^{-1}) brought an inhibition stronger than that of (－)-baclofen alone. **CONCLUSION**: Car facilitates the effects of GABA on pyramidal cells in hippocampal CA1 region, probably related to $GABA_B$ receptors.

The mechanism of the anticonvulsant carbamazepine (Car) is not clear[1,2]. There were some evidences indicating the action of Car is related to GABA system. For instance, picrotoxin, a GABA-regulated chloride ion channel blocker, could work against the taming effect of Car on footshock-induced fighting in mice[3]. Chronic administration of Car increased the GABA concentration in some brain regions of the rat[4,5]. Moreover, alteration of GABA receptors in rat brain was seen after chronic treatment with Car, and the density of $GABA_B$ receptors was enhanced in the hippocampus[6]. The present work was undertaken to examine the interactions of Car with GABA in rat hippocampus *in vitro*.

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MATERIALS AND METHODS

Sprague-Dawley ♂ rats weighing 160 － 200 g were decapitated and the brains were placed in ice-cold Krebs-Ringer solution (NaCl 124, KCl 5, KH_2PO_4 1.24, $MgSO_4$ 1.3, $CaCl_2$ 2.6, and glucose 10 mmol·L^{-1}) gassed with 95 % O_2 + 5 % CO_2. Parasagittal slices containing hippocampus (350 μm) were preincubated in Krebs-Ringer solution at 35 ℃ for 90 － 120 min.

Slices were transferred to a chamber for recording field potentials and perfused with Krebs-Ringer solution at 1.3 mL

· min^{-1}. Stimulation (0.5 Hz and 50 μs) was applied through a bipolar stainless steel electrode to Schaffer collaterals. Field potentials were recorded from pyramidal cells in CA1 with glass micropipettes (3 – 5 MΩ) filled with Krebs-Ringer solution (Fig 1).

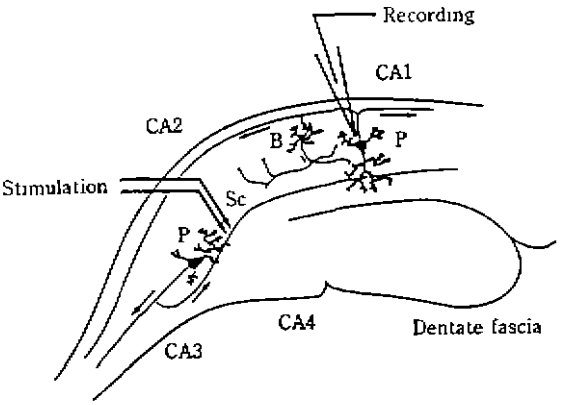

Fig 1. Stimulation and recording on rat hippocampus slice. B = basket cell; P = pyramidal cell; Sc = Schaffer collateral.

Car (Sigma), GABA (Wako Chemic Co, Japan), bicuculline (Wako Chemic Co) or (–)-baclofen (Sigma) were added in perfusing fluid individually or in combination. The amplitude of field potentials was recorded.

RESULTS

Effects of GABA and Car on field potentials

GABA (0.1 – 1 mmol·L^{-1}) concentration-dependently reduced the amplitude of potentials (Fig 2). Car <0.3 mmol·L^{-1} did not reduce field potentials but Car 0.3 mmol·L^{-1} began to depress the amplitude of field potentials (Fig 3).

Interactions between Car and GABA Car 0.2 mmol·L^{-1} together with GABA (0.1 – 1 mmol·L^{-1}) depressed field potentials more effectively than GABA alone (Fig 2, Fig 4A,B). GABA 0.5 mmol·L^{-1} together with Car 0.1 – 0.3 mmol·L^{-1} gave rise to a distinct graded inhibition on field potentials (Fig 3).

Neither the same concentration of bicuculline as that of GABA (eg, both 0.3 mmol·L^{-1}), nor about twice GABA concentration of bicuculline (eg, GABA 0.3 mmol·L^{-1} with bicuculline 0.5 mmol·L^{-1}) reversed the depressed field potentials. It has been tested in other experiments[7] that this bicuculline (same batch) can reverse inhibition of GABA alone on field potentials recorded in CA1 pyramidal cells of the rat hippocampus.

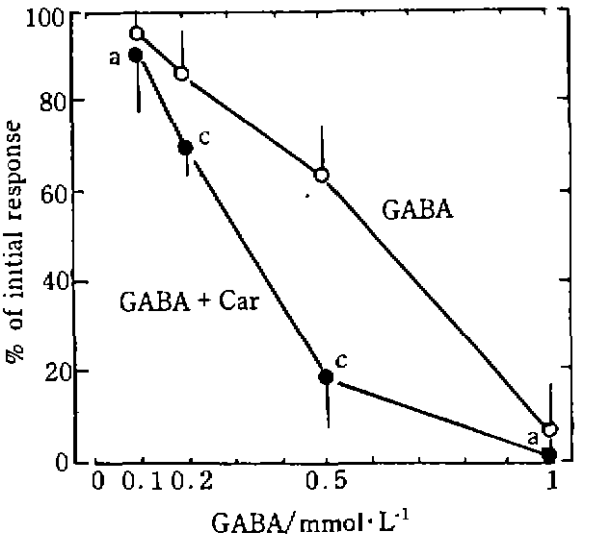

Fig 2. Amplitudes of field potentials after GABA (○), and GABA plus Car 0.2 mmol·L^{-1} (●) recorded from CA1 pyramidal cells.
n = 8 rats, $\bar{x} \pm s$. $^aP<0.05$, $\bar{x} \pm s$. $^cP<0.01$.

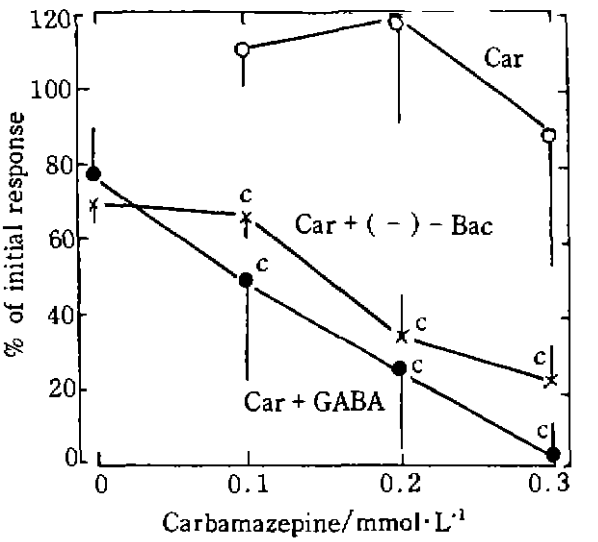

Fig 3. Amplitudes of field potentials after Car alone (○), Car plus GABA 0.5 mmol·L^{-1} (●) and plus (–)-baclofen 2 μmol·L^{-1} (×) recorded from CA1 pyramidal cells.
n = 6 rats, $\bar{x} \pm s$. $^cP<0.01$.

Interaction between Car and (–)-baclofen

Effect of (–)-baclofen appeared to be stronger than that of GABA because (–)-baclofen 1 – 5 μmol·L^{-1} resulted in a similar inhibition to that observed with GABA 0.1 – 1 mmol·L^{-1} (Fig 2, Fig 5). Car (0.2 mmol·L^{-1}) together with (–)-baclofen

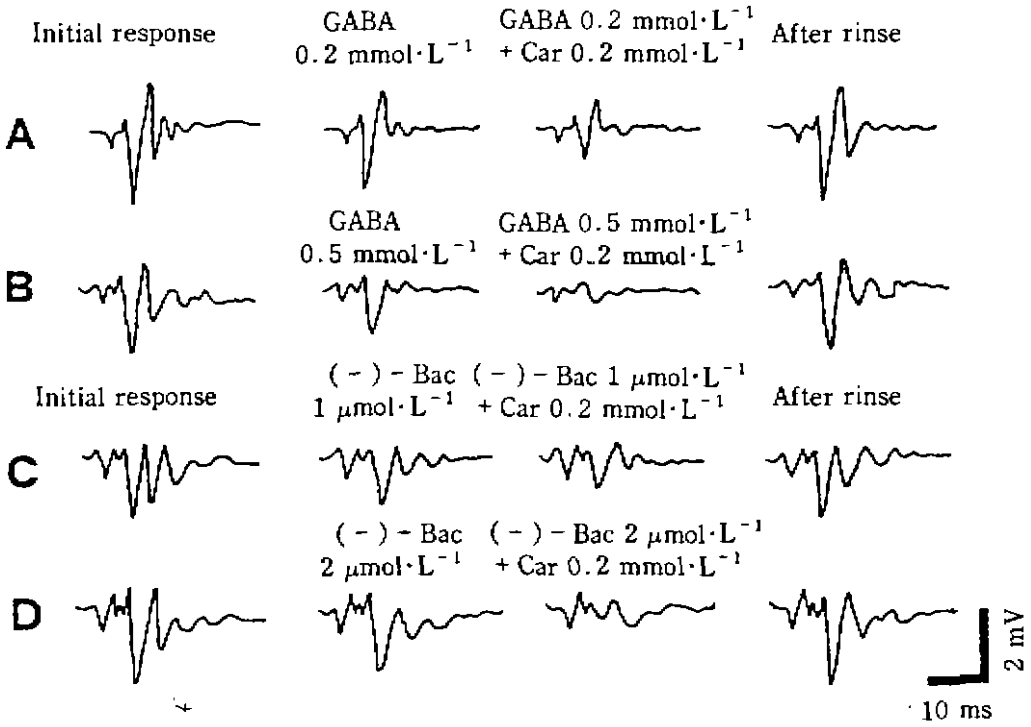

Fig 4. Facilitation of carbamazepine (Car) on GABA (A,B) and (-)-baclofen (C, D) in depressing field potentials.

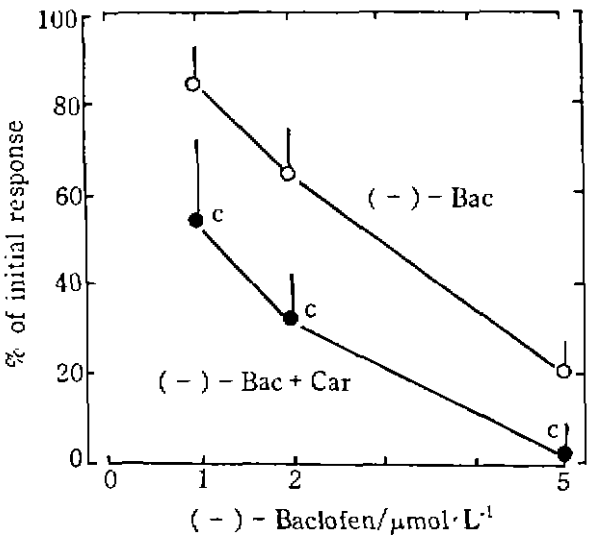

Fig 5. Amplitudes of field potentials after (-)-baclofen alone (○), and plus Car 0.2 mmol·L⁻¹ (●) recorded from hippocampal CA1 pyramidal cells.
***n* = 4 rats. $\bar{x} \pm s$. °*P* < 0.01.**

(1 - 5 μmmol·L⁻¹) had also facilitated inhibitory effect of (-)-baclofen on field potentials (Fig 4C, D, Fig 5). Dose dependent reduction of potentials by Car (0.1 - 0.3 mmol·L⁻¹) was induced with (-)-baclofen 2 μmol·L⁻¹ (Fig 3).

DISCUSSION

Car 0.2 mmol·L⁻¹ did not show any inhibitory effect on field potentials recorded from CA1 region, but when it was combined with GABA, the inhibition was significantly stronger than GABA alone. Effects of GABA on field potentials of CA1 region are probably brought about through both $GABA_A$ and $GABA_B$ receptors or either of them. Failure of bicuculline to reverse the inhibition induced by GABA together with Car might be accounted for 1) that Car enhanced affinity of GABA to $GABA_A$ receptors and hence bicuculline became less competitive with GABA; 2) otherwise such effects was brought about through $GABA_B$ receptors; 3) involvement of other ionic current.

In the present work (-)-baclofen, an agonist of $GABA_B$ receptor, in combination with Car had shown a positive result similar to that of GABA with Car. It was reported that in hippocampus a kind of

G protein coupled $GABA_B$ receptors, which mediated an outword K^+ current, were located postsynaptically[8]. Those $GABA_B$ receptors might also be involved in depression of field potentials by (−)-baclofen in the present study. Although we can not exclude the involvement of $GABA_A$ receptor or other ionic channels in pharmacologic action of Car, we suppose that the facilitation of Car to GABA in depressing the field potentials recorded from the pyramidal cells is related to $GABA_B$ receptors. This is based on our own observation in the present work and the previous demonstration that Car did not affect GABA induced chloride current[9]. However, this study is far from perfect. $GABA_B$ receptor antagonist phaclofen should have been used to reverse the Car facilitated inhibition of (−)-baclofen. Further researches using more reagents including some channel blockers in the slice study or using patch clamp technique are necessary.

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卡马西平增强 γ-氨基丁酸对大鼠脑片的作用

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关键词 卡马西平; γ-氨基丁酸; 巴氯芬; 海马; 诱发场电位

目的: 研究卡马西平(Car)对 γ-氨基丁酸(GABA)在海马区域作用的影响. **方法**: 在海马脑片(350 μm)上刺激(0.5 Hz, 50 μs) Schaffer 氏纤维, 记录 CA1 区锥体细胞的诱发场电位. **结果**: Car 0.2 mmol·L^{-1}对 CA1 区锥体细胞的诱发场电位没有明显影响, 但 Car 0.2 mmol·L^{-1}和 GABA (0.1 − 1 mmol·L^{-1})同用抑制场电位作用比单用 GABA 时显著增强. Bicuculline 不能翻转被 Car 加强的 GABA 的抑制作用. 继而, 左旋巴氯芬抑制场电位作用强于 GABA. Car 0.2 mmol·L^{-1}和左旋巴氯芬(1 − 5 μmol·L^{-1})同用抑制场电位作用比单用左旋巴氯芬时显著增强. **结论**: Car 增强 GABA 对海马 CA1 区锥体细胞的抑制作用, 其作用机制可能与 $GABA_B$ 受体有关.