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Effects of sigma and phencyclidine receptor ligands on electric field-stimulated rabbit ear artery constriction *in vitro*[1]

BAO Wei-Li, ZHEN Fu-Chun, SUN Feng-Yan, ZHANG An-Zhong
(*Department of Neurobiology, Shanghai Medical University, Shanghai 200032, China*)

ABSTRACT Several ligands of phencyclidine (Phe) receptors: Phe, dizocilpine maleate (Diz, MK-801), 1-[1-(2-thionyl)cyclohexyl] piperidine (TCP), and ligands of sigma (σ) receptors: *dl*-*N*-allylnormetazocine (*dl*-SK&F-10047), 1, 3-di-*ortho*-tylyl-guanidine (DTG), *dl*-pentazocine, were tested on rabbit ear arteries *in vitro*. It was found that the ligands of Phe receptors enhanced the electric field stimulated vasoconstriction (ESV). Their concentration-effect curves of these compounds were parallel in the order of potencies: Phe > Diz > TCP. The ligands of σ receptors had no effect on ESV of the arteries, but 5 μmol·L^{-1} reduced or increased the effect of Phe (5 μmol·L^{-1}) on ESV. *d*-SK&F-10047, *d*-pentazocine, and DTG inhibited the effect of Phe on ESV from 364±22 mg to 142±49 mg (n=5, P<0.01), 262±95 mg (n=5, P<0.05), and 291±80 mg (n=5, P>0.05), respectively. The levoisomers: *l*-SK&F-10047 and *l*-pentazocine enhanced the effect of Phe on ESV from 364±22 mg to 484±78 mg (n=5, P<0.05), and 466±95 mg (n=5, P<0.05), respectively. These results revealed that there were mainly Phe receptors but hardly any σ receptors in the arteries.

KEY WORDS arteries; electric stimulation; vasoconstriction; phencyclidine receptors; sigma receptors; ligands; phencycline; dizoclipine maleate; pentazocine

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Two major classes of compounds are known to produce psychotomimetic effects in humans: the benzomorphans, including the prototypic σ receptor ligand SK& F-10047, and the arylcyclohexylamines, including the widely abused drug phencyclidine (Phe). These 2 classes exhibited similar properties in animal behavior studies, and might share certain physiologic properties[2]. These commonalities have led to the suggestion that these 2 classes acted at a single receptor binding site in the brain. However, recent studies demonstrated the presence of 2 distinct binding sites distinguished by different drug selectivity profiles[3]. These distinct binding sites were the σ receptors, characterized by its receptor-specific ligands 3-[3-hydroxyphenyl]-*N*-(1-propyl)-piperidine (*d*-3-PPP) and 1,3-di-*ortho*-tylyl-guanidine (DTG), and the Phe receptors, characterized by its receptor-specific ligands 1-[1-(2-thionyl)cyclohexyl] (TCP) and dizocilpine maleate (Diz, MK-801). The present study attempted to determine the effects of Phe receptors and σ receptors on the electric field stimulated constriction in the rabbit ear artery.

MATERIALS AND METHODS

Drugs Phe was prepared by Dr SUN Feng-Yan in the School of Pharmacy, Shanghai Medical University. TCP was bought from Beijing Fang-Hua Research Institute. Diz was kindly supplied by Dr L L Iversen (Merck Sharp & Dohme Research Centre, UK) *dl*-SK&F-10047, *dl*-pentazocine, DTG, and *d*-3-PPP were amiably afforded by Du Pont Co, USA.

Rabbits New Zealand rabbits of either sex bred by Shanghai Medical University (n = 15, weighing

12.8± 0.2 kg) were used.

Artery preperation The central ear artery of rabbit was set up in a 4-ml organ bath containing Krebs solution bubbled with 95 % O_2 ± 5 % CO_2 at 37℃. The contraction of artery was induced by electric field stimulation (25—30 V, 5—10 Hz, trains of 5 pulses, 1 ms per pulse, 2.5 min interval). The artery was allowed to equilibrate for 4—5 h prior to receiving electric field stimulation, while the bath medium was changed every 20 min. Concentration-response curves were constructed by increasing the ligand concentrations cumulatively. The concentration was increased only when the previous one produced its maximal effect and remained constant.

Statistical analysis Statistical significance was calculated by the *t* test.

RESULTS

Effects of Phe and σ receptor ligands on electric field-stimulated vasoconstriction (ESV) Phe concentration-dependently (from 0.1 to 5 μmol·L^{-1}) enhanced the ESV in rabbit ear arteries. When the Phe concentration was increased to yield a maximal effect about 364±22 mg, the arterial response to electrical stimulation dropped abruptly. TCP and Diz, both being Phe receptor-specific agonists, showed a similar action, and the order of potencies was Phe > TCP > Diz. The σ receptor ligands: *dl*-SK&F-10047, DTG, and *dl*-pentazocine had little effect on the ESV, but *d*-3-PPP increased the baseline tension of arteries in a concentration-dependent manner with the minimal effective concentration of 1 μmol·L^{-1} (Fig 1).

Effects of σ receptor ligands on vasoconstriction induced by Phe The prototypic σ receptor agonists *d*-SK&F-10047 and *d*-pentazocine at a concentration of 5 μmol·L^{-1} inhibited the effect of Phe (5 μmol·L^{-1}) on ESV from 364±22 mg to 142±49 mg ($n=5$, $P<0.01$) and 262±95 mg ($n=5$, $P<0.05$), respectively. The selective σ receptor agonist DTG had no significant influence on the effect of Phe ($n=5$, $P>0.05$). *l*-SK&F-10047, and *l*-pentazocine at the concentration of 5 μmol·L^{-1} enhanced the effect of Phe on ESV from 364±22 mg to 484±78 mg ($n=5$, $P<0.05$) and to 466±95 mg ($n=5$, $P<0.05$) respectively (Tab 1).

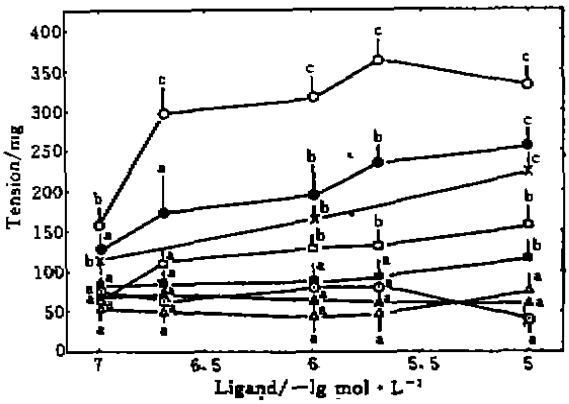

Fig 1. Effects of Phe-receptor ligands Phe (○), Diz (●), TCP (×) and σ-receptor ligands *l*-SK&F-10047 (□), (*l*) pentazocine (■), DTG (△), (*d*) pentazocine (▲), *d*-SK&F-10047, (○) on electric field-stimulated vasoconstriction on rabbit ear artery. $n=5$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* control.

Tab 1. Effects of sigma-receptor ligands (5 μmol·L^{-1}): *d*-SK&F-10047, *l*-SK&F-10047, *d*-pentazocine, *l*-pentazocine, DTG on the electric field-stimulated vasoconstriction enhanced by Phe (5 μmol·L^{-1}). $n=5$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* Phe.

Ligand	Tension/mg
Phe	364±22
Phe + *d*-SK&F-10047	142±49^c
Phe + *l*-SK&F-10047	484±78^b
Phe + *d*-pentazocine	262±95^b
Phe + *l*-pentazocine	466±95^b
Phe + DTG	291±80^c

DISCUSSION

Our results showed that the ligands of Phe receptor could enhance the ESV but those of σ receptor did not exhibit such an effect.

These data suggested that Phe and σ receptors were 2 different kinds of receptor, and the Phe receptors existed mainly in the peripheral arteries. These findings were in accordance with those from the brain of cat and other animal species using bindings and autoradiography[4,5].

The ligands of σ receptor showed no effect on ESV. Yet, they had various influences on the effect of Phe. Though *d*-SK&F-10047 did label both σ and Phe sites, it was 10-fold more potent at σ sites than at Phe sites[4]. It seemed likely that in modest dosage it might interact primarily with the σ sites. Therefore, *d*-SK&F-10047 had no effect on ESV, but did have some effect on the action of Phe. DTG, and *d*-3-PPP revealed high selectivity for σ binding sites, having effect neither on ESV, nor on the effect of Phe. Since the regional distribution of the Phe receptor was different from that of the σ binding sites[1,5], it was not possible that Phe and σ binding sites were different sites on the same receptor. We suggested that cooperation of *l*-SK&F-10047 with vasoconstriction of Phe and antagonistic effect of *d*-SK&F-10047 on the vasoconstriction of Phe were via the Phe receptor interaction, and that *d*-3-PPP from 10^{-8} to 10^{-6} mol·L^{-1} had no effect on ESV in rabbit ear artery, but it increased the baseline tension of blood vessels with a minimal effective concentration of 10^{-6} mol·L^{-1}. Some evidences illustrated that there were multiple sites for *d*-3-PPP in blood vessels[6]. The results suggested that the excitatory effect of *d*-3-PPP on baseline tension of the blood vessls might be by means of other pathways. In conclusion, Phe and σ receptor might not be of the same type, there were mainly Phe receptors but hardly any σ receptors in the peripheral blood vessels.

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Sigma 和苯环利定受体的配体对电场刺激引起兔耳血管收缩的作用

包维丽，郑付春，孙凤艳，张安中 (上海医科大学神经生物学教研室，上海200032，中国)

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摘要 用生物鉴定法研究苯环利定 Phe 受体的配体 Phe，TCP，Diz 及 σ 受体的配体 *dl*-SK&F-10047 *dl*-pentazocine，DTG 在兔耳中动脉的作用。结果表明：Phe 受体配体均能剂量依赖地增强电场刺激引起的动脉收缩；而 σ 受体配体无此作用。右旋的 σ 受体配体能抑制 Phe 的作用；它的异构体却是增强 Phe 作用。提示：在外周血管上主要存在 Phe 受体。

关键词 动脉；电场刺激；血管收缩；苯环利定受体；σ 受体；配位体；苯环利定；dizoclipine maleate；喷他佐辛