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β-Endorphin- and GABA-mediated depressor effect of specific electroacupuncture surpasses pressor response of emotional circuit

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Abstract

It has been proved that input of specific electroacupuncture (EA) can activate β-endorphin(β-EP)ergic and noradrenergic neurons projecting to the rostral ventrolateral medulla (RVL), the latter acting upon the RVL-GABAergic interneurons, thereby produce depressor effect. The present study further shows that: (1) The EA depressor effect is strong enough to surpass the pressor response of the AC (nucleus amygdaloideus centralis)-emotional circuit, (2) both β-endorphin (β-EP) and GABA in the RVL mediate the EA antagonistic effect, (3) the EA effect does not take place in the AC and paraventricular nucleus (two key nuclei besides the RVL, which also have β-EPergic input) in the emotional circuit.

Keywords: Blood pressure; Emotion; Stress; Central nervous system; β-Endorphin; GABA; Acupuncture

1. Introduction

Essential hypertension is one of the most common disorders affecting human health. Prolonged emotional stress is an important factor in the development of neurogenic hypertension [1], but its mechanism is still unclear. We have done a series of studies on mechanisms underlying pressor responses of brain nuclei controlling emotion and stress [8,15,20,22,23,29–31], the results prove that there is a pressor neural circuit composed of nuclei controlling emotion and stress, which may be the neurophysiological basis of prolonged emotional stress inducing hypertension. The nucleus amygdaloideus centralis (AC) widely connecting with the other nuclei is the most important, for details see Fig. 3 in Discussion.

There are two groups of β-endorphinergic (β-EPergic) neurons in the brain, one in the nucleus arcuatus (AR) [14] and the other in the nucleus tractus solitarii (NTS) [13]; both groups projecting to the rostral ventrolateral medulla (RVL) have the depressor and bradycardia function [6]. Our previous study [17] showed that input of the specific electroacupuncture (EA) could activate not only (β-EPergic neurons in the AR and NTS in sequence [17], but also noradrenergic neurons in the A_5 and A_1 areas, the latter acting upon GABAergic interneurons in the RVL [11]; thereby inhibit RVL-sympathoexcitatory neurons and produce depressor effect. The purpose of the present study was firstly to examine whether the depressor effect of this specific electroacupuncture (EA) was strong enough to surpass the pressor response of the neural circuit composed of nuclei controlling emotion and stress, and secondly to analyze mechanisms underlying it. Hence in the present study the following experiments were carried out: 1) during the specific EA stimulation the pressor response of the AC (the most important nucleus in the emotional pressor circuit) to glutamate (Glu) was examined to see whether it was affected by the EA, since the β-EPergic neurons in the AR have long axons projecting nearly to all brain areas [5], and the AC contains β-EPergic fibers [14]; 2) cardiovascular effect of β-EP injection into the AC, and effect of β-EP antiserum (β-EP AS) preinjected into the AC on the EA depressor response were tested; 3) cardiovascular effect of (β-EP injected into either the nucleus paraventricularis (NPV) or RVL (two final efferent nuclei in the AC-emotional pressor circuit), and effect of β-EP AS injected into the NPV or RVL on the cardiovascular response of AC excitation during EA (EA-AC response) were observed; 4) Effect of bicuculline (a GABA antagonist) preinjected into the RVL on the EA-AC response was also examined.

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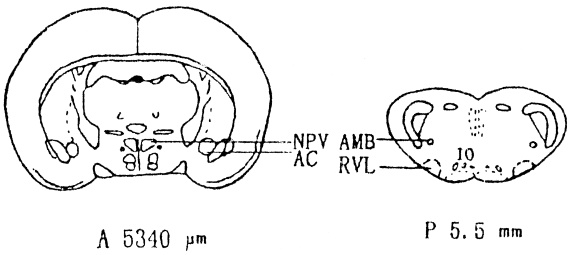

Fig. 1. Schematic coronal sections of the brain showing nuclei injected. Abbreviations: AC, nucleus amygdaloideus centralis; NPV, nucleus paraventricularis; RVL, rostral ventrolateral medulla; IO, nucleus olivaris inferior; AMB, nucleus ambiguus.

2. Method

2.1. Preparation of animals

Experiments were performed on male Wistar rats (total number: 41) weighing 180 ~ 310 g, anesthetized with urethane (1.5 g/kg, IP). After insertion of a tracheal cannula and an arterial catheter, the rat was mounted in a stereotaxic apparatus, and the relevant brain surface was exposed by craniotomy for inserting the microinjection cannula later. The animal was then paralyzed with tubocurarine (2 mg/kg, IP) and artificially ventilated to prevent respiratory influence on blood pressure. The rectal temperature was monitored and maintained at 37 ± 0.5° C. The mean arterial pressure (AP) was directly measured with a blood pressure transducer (model YT-2) and recorded on a recorder (model XWC-200A), from the catheter inserted into the right carotid artery; the heart rate (HR) was monitored and measured by electrocardiography (for details see Ref. 25).

2.2. Location of nuclei (Fig. 1)

For forebrain nuclei, the coordinate system of Jacobowitz and Palkovits [12] was used. The coordinates were as follows. AC: A 4110~5660 μm, LR 4.2 mm, 6.8 mm below the cerebral surface; NPV: A 5340~5660 μm, LR 0.3 mm, 6.8 mm below the brain surface. For the RVL coordinate system of Palkovits and Jacobowitz [24] was used. RVL: P 5.0~5.5 mm, LR 2.0 mm, 7.8 mm below the cerebellar surface. The tip of the injection-cannula was just located on the dorsal border of the nucleus in order to avoid damage.

2.3. Microinjections

The following drugs were injected: monosodium L-glutamate (Glu, Sigma): 11.2 μg/0.3 μl (for the AC); β-endorphin (β-EP, Sigma): 0.6 μg/0.3 μl (for the AC), 0.4 μg/0.2 μl (for the NPV and RVL), these drugs were dissolved in normal saline; β-endorphin antiserum (β-EP AS, Second Military Medical College, Shanghai, China) was diluted by normal serum, titer: 1:6000, 0.2 μl/site (but 0.3 μl/site for the AC), which has no cross-reactivity with α-endorphin, γ-endorphin, methionine-enkephalin, leucine-enkephalin, dynorphin A 1–13, dynorphin B, neurotensin, somatostatin, vasopressin and oxytocin; bicuculline (Bicu, Sigma): 0.08 μg/0.2 μl. 0.9% NaCl or normal serum (injection volume being identical with the corresponding drug) was used as control. All drugs were delivered over a period of 10 s via a stainless steel cannula (outer diameter 0.4 mm, inner diameter 0.2 mm). One kind of antagonist was used in each rat, and in most experiments each animal served as his own control. Usually, the EA antagonistic effect was tested 8–13 min after injection of antagonist.

2.4. Electroacupuncture

Two stainless steel needles were inserted into "Tinggong (SI 19)" and "Quchi (LI 11)" on each side. Electrical stimulation (3 V, 0.5 ms duration and 2 Hz, lasting for 30 s) was delivered via two needles by a medical pulse stimulator (model DM) which was produced by Hai Dian Medical Electron-instrument Factory in Beijing (For details see Ref. 16 and 17).

2.5. Histological procedures

At the end of each experiment, the animal was perfused with 100 ml of 0.9% NaCl followed by 100 ml of 10% formalin. After the brain was fixed, a standard coronal cut paralleling to the injection cannula was made, then the brain was removed and attached on a freezing microtome, frozen sections were cut at 100 μm in the frontal plane. Injection sites (at the tip of the injection cannula track) were identified histologically in sections stained with cresyl violet. Only the results from injection sites being located at the dorsal border of the relevant nuclei were included in data analysis, whereas the results from injection sites within nuclei that may produce damage, and outside nuclei were excluded.

2.6. Statistical analysis

Data are shown as mean ± SEM. Significance of differences was tested with paired *t* test (only when the antagonist was used, under such condition each animal served as his own control.) or *t* test (two tailed) for comparisons between separate control and experimental groups (when the antagonist was not used, each animal did not serve as his own control).

3. Results

3.1. Cardiovascular effect of Glu-injection into the AC and that effect during EA

Glu-injection into unilateral AC induced a pressor response (Δ 8.4 ± 0.9 mmHg, n = 7) which was reversed

Table 1
Effect of electroacupuncture (EA) on pressor response of nucleus amygdaloideus centralis (AC) to glutamate and effect of β-endorphin antiserum preinjected into the AC (i. AC) on depressor response of EA

Group	n	Arterial pressure (mmHg)		Heart rate (beats/min)	
		Baseline	Change	Baseline	Change
1. EA	9	95.6 ± 3.8	−11.8 ± 1.2	411.2 ± 12.2	5.4 ± 3.6
2. Glu (i.AC)	7	90.6 ± 3.6	8.4 ± 0.9	375.6 ± 4.4	12.6 ± 5.3
Glu (i.AC) + EA	6	86.1 ± 4.4	−7.5 ± 1.9**	390.0 ± 5.7	2.2 ± 4.0
3. NSR (i.AC)	6	98.9 ± 5.1	0.3 ± 0.4	434.9 ± 5.5	2.1 ± 2.1
β-EP AS (i.AC)	6	99.8 ± 3.5	0.1 ± 0.9	455.1 ± 13.3	0.3 ± 0.9
4. EA after NSR (i.AC)	10	103.0 ± 2.3	−9.6 ± 1.4	449.6 ± 9.4	11.9 ± 2.9
EA after β-EP AS (i.AC)	10	100.4 ± 2.1	−10.1 ± 1.6	470.5 ± 10.5	10.9 ± 1.8

NSR, normal serum.
** $P < 0.01$ as compared with the corresponding control group.

when EA was delivered at the same time (Δ -7.5 ± 1.9 mmHg, Table 1), indicating that the depressor effect of EA is strong enough to surpass the AC pressor response.

Because the amplitude of the heart rate (HR) response was small and variable, in the following experiments we mainly analyze the arterial pressure (AP) response.

3.2. Cardiovascular effect of β-EP injected into the AC, and effect of β-EP AS preinjected into bilateral AC on EA depressor response

Fig. 2 shows that β-EP injected into unilateral AC ($n = 6$) had no significant effect on AP and HR (Δ 0.0 ± 0.7 mmHg and Δ 0.9 ± 0.9 beats/min, bpm). (β-EP AS injected into bilateral AC alone had no effect on AP and HR (Table 1), (β-EP AS preinjected into bilateral AC also did not significantly affect the effect of EA (in Table 1, the experimental group: Δ -10.1 ± 1.6 mmHg and 10.9 ± 1.8 bpm, the control group: Δ -9.6 ± 1.4 mmHg and Δ 11.9 ± 2.9 bpm).

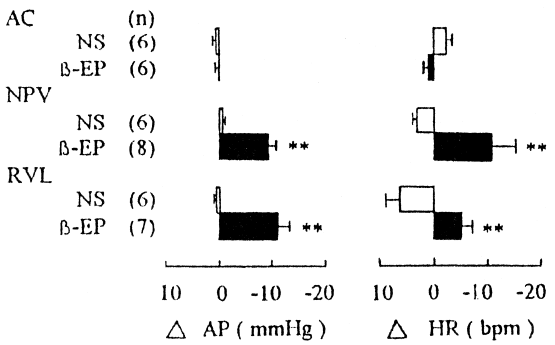

Fig. 2. Cardiovascular effects of normal saline (NS) and β-endorphin (β-EP) microinjected into the nucleus amygdaloideus centralis (AC), nucleus paraventricularis (NPV) or rostral ventrolateral medulla (RVL).

3.3. Cardiovascular effects of β-EP injected into either the RVL or NPV, and effect of β-EP AS preinjected into bilateral RVL or NPV on response of Glu-injection into the AC accompanied with EA

β-EP injection unilaterally into either the RVL or NPV evoked a depressor response (Fig. 2). β-EP AS injection into bilateral RVL or NPV alone had no significant effect on AP and HR (Table 2). However, β-EP AS preinjection into bilateral RVL nearly abolished the EA-antagonistic effect on the AC pressor response (in control group: Δ -7.8 ± 1.0 mmHg, in experimental group: Δ 3.5 ± 1.3 mmHg), whereas β-EP AS preinjection into bilateral NPV have no effect (in control group: Δ -9.2 ± 2.0 mmHg, in experimental group: Δ -10.0 ± 1.4 mmHg; Table 2), indicating that in normal condition there is no tonic β-EP release, and the specific EA mainly induces an increase of β-EP release in the RVL (not in the NPV), thus antagonizing the AC pressor response.

3.4. Effect of GABA antagonist preinjected into bilateral RVL on response of Glu-injection into the AC accompanied with EA

It is well known that GABA delivered to the RVL produces a remarkable decrease in AP. In the present study bicuculline (a GABA antagonist) injection into bilateral RVL alone elicit a marked increase in AP (Δ 36.6 ± 6.5 mmHg) and HR (Δ 15.4 ± 3.8 bpm), 8∼13 min later when AP returned to the normal level, the EA-antagonistic effect on the AC pressor response to Glu was reversed from Δ -8.6 ± 0.8 mmHg (in the control group) to Δ 8.1 ± 1.9 mmHg (in the experimental group) (Table 2), indicating that in normal condition there is a tonic GABA release in the RVL, and the specific EA further increases the GABA release, thus produces depressor effect. This is another mechanism underlying the EA antagonistic effect on the AC pressor response.

Table 2
Effect of β-endorphin antiserum (β-EP AS) or bicuculline (Bicu) preinjected into bilateral nucleus paraventricularis (i. NPV) or rostral ventrolateral medulla (i. RVL) on cardiovascular response of AC-excitation by glutamate (Glu) accompanied with electroacupuncture (EA)

Group	n	Arterial pressure (mmHg)		Heart rate (beats/min)	
		Baseline	Change	Baseline	Change
NPV					
1. NSR (i.NPV)	7	95.8 ± 5.2	−1.8 ± 1.4	433.1 ± 16.8	3.7 ± 2.9
β-EP AS (i.NPV)	7	90.5 ± 4.7	−2.3 ± 2.4	422.3 ± 19.7	1.3 ± 3.4
2. Glu (i.AC) + EA					
after NSR (i.NPV)	6	95.3 ± 6.5	−9.2 ± 2.0	441.2 ± 21.2	0.8 ± 1.1
Glu (i.AC) + EA					
after β-EP AS (i.NPV)	6	87.4 ± 4.9	−10.0 ± 1.4	420.7 ± 23.1	6.7 ± 1.3**
RVL					
1. NSR (i.RVL)	8	105.4 ± 5.4	−2.2 ± 1.4	400.0 ± 17.6	0.7 ± 3.1
β-EP AS (i.RVL)	8	97.0 ± 5.6	1.9 ± 2.4	392.9 ± 15.2	−2.0 ± 3.2
2. Glu (i.AC) + EA					
after NSR (i.RVL)	6	92.9 ± 4.1	−7.8 ± 1.0	427.5 ± 12.5	2.8 ± 2.3
Glu (i.AC) + EA					
after β-EP AS (i.RVL)	6	90.6 ± 4.7	3.5 ± 1.3**	429.0 ± 17.3	8.2 ± 4.2
3. NS (i.RVL)	7	106.7 ± 4.0	−0.3 ± 0.7	425.2 ± 17.5	−3.0 ± 2.5
Bicu (i.RVL)	7	108.1 ± 3.8	36.6 ± 6.5**	411.7 ± 20.4	15.4 ± 3.8**
4. Glu (i.AC) + EA					
after NS (i.RVL)	6	104.1 ± 2.9	−8.6 ± 0.8	472.9 ± 6.1	2.4 ± 1.6
Glu (i.AC) + EA					
after Bicu (i.RVL)	6	133.6 ± 3.9	8.1 ± 1.9**	453.7 ± 9.4	2.9 ± 2.7

NSR, normal serum; NS, normal saline.
** $P < 0.01$ as compared with the corresponding control group.

4. Discussion

4.1. Regarding experimental method

The rationale for using anesthetic and muscle relaxant, each animal serving as his own control, and using glutamate to excite the AC, etc. has been discussed elsewhere (see Ref. 31). Hence it will not be discussed here again.

4.2. The pressor circuit composed of nuclei controlling emotion and stress

Many nuclei in the brain are involved in emotion, stress or defense reaction: such as the AC [7] lateral hypothalamus/perifornical region (LH/PF) [27], nucleus ventromedialis and nucleus dorsomedialis (NVM and NDM) [28], NPV [4], periaqueductal gray matter (PAG) [2], nucleus parabrachialis (NPB) [21] and locus coeruleus (LC) [19]. Among the above mentioned pressor nuclei the AC is the most important one: The AC mediates conflict behavior [26], autonomic and behavioral responses related to conditioned fear [18], emotional autonomic and behavioral reactions to noxious events [3]; and this nucleus is also involved in the cardiovascular response evoked by acoustic conditioned emotional stimuli [9]. Bilateral lesions of the AC during the prehypertensive stage inhibited the development of the high blood pressure in the spontaneously hypertensive rats [10]. Moreover, the AC widely connects with other nuclei controlling emotion and stress, results of a series of our studies [8,15,20,22,23,29–31] prove that the AC links the other emotional pressor nuclei functionally, thus composing a pressor neural circuit (see Fig. 3) which may be the neurophysiological basis of prolonged emotional stress inducing hypertension.

4.3. Mechanisms underlying depressor effect of the specific EA in antagonism to pressor effect of the AC-emotional circuit (Fig. 3)

As mentioned in the Introduction, our previous studies have proved that "Tinggong" (SI 19) is a novel acupoint for 2 Hz EA-induced depressor response [16]. Input of this specific EA can activate β-EPergic neurons (in the AR and NTS) [17] and GABAergic RVL-interneurons (via A_5 and A_1 areas) [11], both kinds of neurons inhibiting the RVL-sympathoexcitatory neurons, thereby producing depressor effect. The present study further showed that the depressor effect of the specific EA could surpass the pressor response of the AC. Injection of either the β-EP AS or GABA antagonist into the RVL could reduce the EA antagonistic effect. Whereas β-EP AS injection into the AC or NPV respectively did not affect the EA antagonistic effect on the AC pressor response significantly, although the β-EPergic neurons in the AR have long axons projecting nearly to all brain areas [5], and both the AC and NPV contain β-EPergic fibers [14]. The results indicate that the EA antagonistic effect is carried out mainly by inhibiting the sympathetic nervous system, and is mediated by β-EP and GABA in the

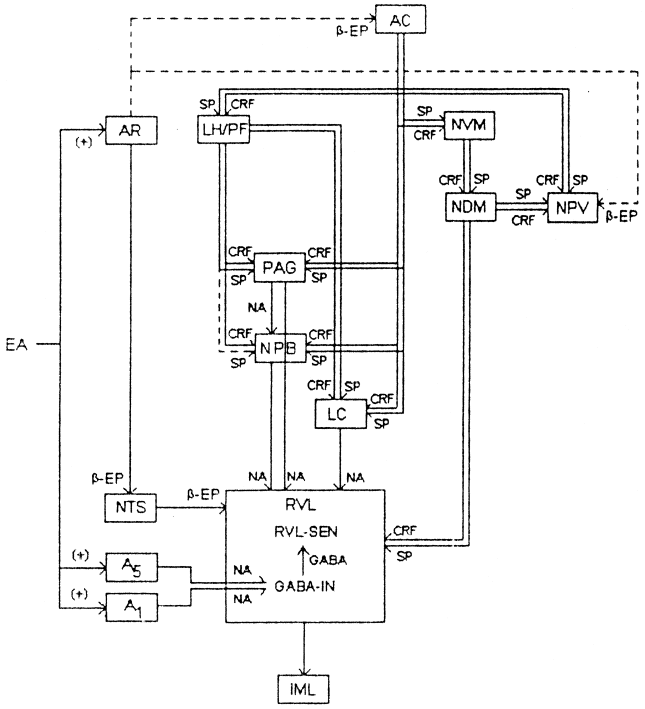

Fig. 3. Diagram showing mechanisms underlying specific electroacupuncture (EA) in antagonism to the pressor effect of the neural circuit composed of the AC and other nuclei controlling emotion and stress. - - - - -, Effect is not significant. Abbreviations: CRF, corticotropin releasing factor; SP, substance P; NA, noradrenaline; β-EP, β-endorphin. AC, nucleus amygdaloideus centralis; LH/PF, lateral hypothalamus/perifornical region; PAG, periaqueductal gray matter; NPB, nucleus parabrachialis; LC, locus coeruleus; NVM, nucleus ventromedialis; NDM, nucleus dorsomedialis; NPV, nucleus paraventricularis; AR, nucleus arcuatus; NTS, nucleus tractus solitarii; A_5, A_5 area; A_1, A_1 area; RVL, rostral ventrolateral medulla; IML, intermediolateral column; RVL-SEN, RVL-sympathoexcitatory neuron; GABA-IN, GABA-interneuron.

RVL, the latter being one of the final efferent nuclei in the AC-emotional circuit, as shown in Fig. 3; it is consistent with the results of our previous studies on mechanisms underlying the depressor effect of the specific EA [11,16, 17]. As for why β-EP AS injection into the AC or NPV could not significantly affect the EA antagonistic effect on the AC pressor response, maybe it is because the effect is very weak, and hence it is concealed by the strong EA effect on the RVL.

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