

## Effect of dexamethasone on cardiovascular response induced by norepinephrine in nucleus tractus solitarii

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**KEY WORDS** dexamethasone; norepinephrine; blood pressure; solitary nucleus; mifepristone; bicuculline

### ABSTRACT

**AIM:** To study the effect of dexamethasone on cardiovascular response induced by norepinephrine (NE) in nucleus tractus solitarii (NTS).

**METHODS:** The variations of cardiovascular action caused by these drugs were observed after injection of mifepristone (Mif), dexamethasone (Dex), bicuculline (Bic), and NE into the medial and intermediate NTS.

**RESULTS:** Microinjection of Dex ( $0.39 \text{ mmol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ ) into the medial and intermediate NTS abolished the vasodepressed response to NE ( $8 \text{ mmol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ ) microinjected into the same area 10 min later, and the inhibition did not disappear until 4 h. The rapid inhibitory effects of Dex on NE vasodepression was not antagonized by Mif ( $4.66 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ ), but it was blocked by Bic ( $3.24 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ ).

**CONCLUSION:** Dex abolished cardiovascular response to NE microinjected into NTS which may be mediated by GABA<sub>A</sub> receptor.

### INTRODUCTION

There was an important inhibitory interaction between catecholamines and glucocorticoids to meet stress situation and even resting

condition<sup>[1-4]</sup>. Corticosterone treatment to intact rats caused a decrease of norepinephrine (NE) activity in brain<sup>[5,6]</sup>. The interaction between them was one important link of the feedback sited in the hypothalamo-pituitary-adrenocortical system to adjust the cardiovascular and metabolic activities. The present study examined the effects of glucocorticoids within the cardiovascular part of the nucleus tractus solitarii (NTS), which contains abundant glucocorticoid receptors<sup>[7]</sup>, on NE involvement with cardiovascular regulation.

### MATERIALS AND METHODS

Adult Wistar rats ( $n = 191$ , body weight 250 - 300 g, Certificate No 0000819) were obtained from Experimental Animal Center, Norman Bethune University of Medical Sciences (Certificate No 960101010). Rats were anesthetized with a mixture of  $\alpha$ -chloralose ( $50 \text{ mg} \cdot \text{kg}^{-1}$  ip) and urethane ( $1 \text{ g} \cdot \text{kg}^{-1}$  ip). The trachea was cannulated so that airway was unobstructed. An heparinized (Heparin  $50 \text{ kU} \cdot \text{L}^{-1}$  in 0.9 % saline) catheter was inserted into the femoral artery and connected to a baroreceptor transducer adapted to a polygraph recorder to monitor blood pressure (BP) and heart rate (HR). Then the rat was placed on a heating pad to maintain rectal temperature at ( $37 \pm 0.5$ ) °C in stereotaxic frame. The rat head was adjusted to 45° angle from the horizontal plane. The electrocautery of the neck muscle was conducted to expose the posterior atlanto-occipital membrane and revealed the caudal medulla in the region of the obex and calamus scriptorius by fine

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dissection.

Unilateral injections were made stereotaxically into the NTS with a glass micropipette (tip diameter 50–60  $\mu\text{m}$ ) connected to a microsyringe by a polyethylene tube, the tip of the pipette was positioned 0.5 mm to the calamus scriptorius, 0.5 mm lateral from the midline and 0.5 mm deep to the surface of brainstem. Dexamethasone 21-phosphate disodium salt (Dex, Sigma, USA), NE (Sigma, USA), and bicuculline (Bic, Sigma, USA) were dissolved in 0.9 % saline (pH 7.2). The antiglucocorticoid mifepristone (Mif) from Roussel-UCLAF (Romainville, France) was dissolved in sesame oil. All drug solutions were delivered in a volume of 0.1  $\mu\text{L}$  over approximately 20 s. Saline or sesame oil was used as control injection.

The study included 3 experiments. Rats of experiment 1 were divided into 3 groups: NE alone injected, Dex groups, and saline groups. Dex (or saline) group meant that NE (0.8 nmol) was microinjected into the NTS different time after injection of Dex (20 ng) (or saline). Experiment 2 included 2 groups: control and Mif groups. The procedure sequence of drug microinjected as follow: Mif (20 ng) (or sesame oil as control) was microinjected into NTS 10 min before Dex (20 ng) microinjected, and NE (0.8 nmol) was administered into the same area 10 min after Dex injected. Experiment 3 contained 2 groups: (saline + Dex) + NE and (Bic 15 ng + Dex) + NE. The procedure sequence of injection was injection of NE (0.8 nmol) 10 min after the coinjection of Dex (20 ng) and Bic (15 ng) (or saline).

Basal values of blood pressure were registered at least 15 min before the injection.

At the end of the experiments, pontamine sky blue 100 nL was injected for verification of injection sites histologically.

Data were expressed as  $\bar{x} \pm s$  and analyzed

by paired *t*-test compared with preinjection.

## RESULTS

**Effect of Dex on the cardiovascular response to NE in NTS** NE alone injected into the medial and intermediate NTS remarkably decreased BP ( $-2.67 \pm 0.21$ ) kPa and HR ( $-35 \pm 11$ ) beats  $\cdot \text{min}^{-1}$  ( $P < 0.01$ ). If NE and Dex (20 ng, the dosage alone could not affect the changes of BP and HR, our unpublished observations) was simultaneously microinjected into NTS, there were significant decreases of BP ( $-2.52 \pm 0.23$ ) kPa and HR ( $-30 \pm 8$ ) beats  $\cdot \text{min}^{-1}$ , ( $P < 0.01$ ). However, 10 min after injection of Dex into the NTS, NE microinjected into the same area did not induce significant decrease in BP ( $-0.13 \pm 0.10$ ) kPa and HR ( $-5 \pm 5$ ) beats  $\cdot \text{min}^{-1}$  ( $P > 0.05$ ), and NE could not evoke significant vasodepression in 4 h. In saline group, the same volume of physiological saline did not affect the cardiovascular response to NE microinjected into the NTS. (Tab 1)

**Rapid inhibitory effect of Dex on cardiovascular response to NE in NTS** Either Mif or sesame oil in 2 groups was microinjected into NTS 10 min before Dex microinjected, injection of NE into the same area did not significantly decrease BP and HR ( $P > 0.05$ , Tab 1). However, 10 min after coinjection of Dex with Bic into NTS (Tab 1), injection of NE into the same area immediately decreased BP and HR [ $(-2.27 \pm 0.25)$  kPa, ( $-27 \pm 10$ ) beats  $\cdot \text{min}^{-1}$ ;  $P < 0.01$ ]. But, 10 min after coinjection of Dex with saline, injection of NE did not evoke significant variations of BP and HR.

## DISCUSSION

The present study showed that microinjection of Dex into the medial and intermediate NTS inhibited cardiovascular response to administra-

**Tab 1. Effect of injection of Dex (20 ng) into NTS on cardiovascular response to NE (0.8 nmol) administered into the same area.**  
\**P* < 0.01 vs preinjection.

Treatment	n	Arterial blood pressure		Heart rate	
		Basal value /kPa	Nadir decrease /kPa	Basal value /beats·min <sup>-1</sup>	Peak decrease /beats·min <sup>-1</sup>
Experiment 1					
NE	10	13.7 ± 0.3	2.67 ± 0.21*	350 ± 16	35 ± 11*
Dex groups					
0	10	13.9 ± 0.4	2.52 ± 0.23*	346 ± 14	30 ± 8*
10 min	12	13.7 ± 0.4	0.13 ± 0.10	341 ± 15	5 ± 5
30 min	11	14.0 ± 0.4	0.27 ± 0.20	345 ± 16	10 ± 5
1 h	10	14.0 ± 0.5	0.27 ± 0.23	361 ± 16	5 ± 5
2 h	10	13.6 ± 0.4	0.40 ± 0.37	352 ± 16	0 ± 1
3 h	10	13.9 ± 0.3	0.27 ± 0.20	350 ± 17	5 ± 5
4 h	10	13.9 ± 0.4	0.40 ± 0.33	348 ± 19	10 ± 10
Saline groups					
0	10	13.7 ± 0.3	2.67 ± 0.21*	350 ± 16	35 ± 11*
10 min	10	13.9 ± 0.3	2.80 ± 0.27*	345 ± 20	30 ± 9*
30 min	10	13.5 ± 0.4	2.40 ± 0.28*	342 ± 17	30 ± 9*
1 h	10	13.3 ± 0.3	2.53 ± 0.32*	360 ± 17	36 ± 11*
2 h	10	13.5 ± 0.4	2.27 ± 0.25*	347 ± 18	35 ± 13*
3 h	10	13.5 ± 0.4	2.93 ± 0.31*	346 ± 15	30 ± 12*
4 h	10	13.6 ± 0.4	2.53 ± 0.29*	350 ± 15	38 ± 7*
Experiment 2					
Sesame oil	8	14.0 ± 0.4	0.33 ± 0.10	370 ± 14	10 ± 8
Mif	10	14.0 ± 0.4	0.27 ± 0.18	378 ± 16	5 ± 5
Experiment 3					
Saline	10	14.0 ± 0.4	0.27 ± 0.23	378 ± 16	0 ± 1.5
Bic	10	14.0 ± 0.5	2.27 ± 0.25*	370 ± 14	27 ± 10*

tion of NE into the same area. Moreover, the inhibitory effects developed in a short latency (10 min), and maintained for 4 h. It indicated that there were rapid and slow inhibitory effects of Dex on cardiovascular response to NE in NTS.

Our study showed that the rapid inhibitory effect of Dex on cardiovascular response to NE in NTS was not blocked by Mif, an antagonist for intracellular glucocorticoid receptor, but by Bic, an antagonist for GABA<sub>A</sub> receptor. Because the rapid effects could be evoked by progesterone and glucocorticoids through potentiating the action mediated by GABA<sub>A</sub> receptor<sup>[8]</sup>, this could not prevented by Mif. Activating GABA<sub>A</sub> receptor in NTS increased BP and decreased depressor reflex<sup>[9]</sup>. Furthermore, adrenergic neurons in

the NTS received GABAergic synapses<sup>[10]</sup>, and NE hypotension had something to do with the functional state of GABAergic system<sup>[11-13]</sup>. It is inferred that the rapid inhibitory effects of Dex on cardiovascular response to NE microinjected into the NTS might be mediated through activating GABA<sub>A</sub> receptor.

In addition, chronic experiments showed that glucocorticoids had effects on the function, affinity and sensitivity of α<sub>2</sub>-adenergic receptor in central neural system, and the effect was different from various area in brain<sup>[14]</sup>. Whether the rapid inhibitory effects of Dex on cardiovascular response to NE microinjected into the NTS is mediated through affecting the function of α<sub>2</sub>-adrenergic receptor is being discussed.

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地塞米松对去甲肾上腺素在孤束核引起的心血管活动的影响  
R977.1  
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- 关键词** 地塞米松; 去甲肾上腺素; 血压; 孤束核; 米非司酮; 荷包牡丹碱 心血管调节
- 目的:** 研究糖皮质激素对去甲肾上腺素在孤束核对心血管活动调节的影响。 **方法:** 向内侧和中间内侧孤束核(NTS)微量注射地塞米松(Dex)、去甲肾上腺素(NE)、米非司酮及荷包牡丹碱(Bic), 观察它们引起的心血管活动的变化。 **结果:** Dex ( $0.39 \text{ mmol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ )可以消除 10 min 后在同一区域注射 NE ( $8 \text{ mmol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ )所引起的血压下降、心率减慢的效应, 这种抑制作用 4 h 内不消失。 其中的快速抑制作用不能被米非司酮 ( $4.66 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ )所拮抗, 但可以被 Bic ( $3.24 \mu\text{mol} \cdot \text{L}^{-1}$ ,  $0.1 \mu\text{L}$ )所阻断。 **结论:** Dex 消除 NE 在 NTS 内引起的心血管效应, 其机制可能通过 GABA<sub>A</sub> 受体来介导。
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