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Short communication

Brain nuclear factor kappa B is involved in the corticotropin-releasing factor-induced central activation of sympatho-adrenomedullary outflow in rats

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Abstract

Using urethane-anesthetized rats, we examined whether an activation of nuclear factor kappa B is involved in the corticotropin-releasing factor-induced increase in plasma levels of catecholamines. An intracerebroventricularly administered corticotropin-releasing factor (1.5 nmol/animal)-induced increase of plasma catecholamines was dose-dependently reduced by pyrrolidine dithiocarbamate (a nuclear factor kappa B antagonist) (1 and 9 nmol/animal, intracerebroventricularly) and SN50 (a peptide inhibiting nuclear factor kappa B translocation) (9 and 18 nmol/animal, intracerebroventricularly), while SN50M (an inactive control peptide for SN50, 19 nmol/animal, intracerebroventricularly) had no effect on the corticotropin-releasing factor-induced elevation of both catecholamines. Furthermore, the corticotropin-releasing factor-induced responses were also attenuated by rosiglitazone (a peroxisome proliferator-activated receptor-γ agonist)(50 nmol/animal, intracerebroventricularly). These results suggest the involvement of brain nuclear factor kappa B in the corticotropin-releasing factor-induced central activation of the sympatho-adrenomedullary outflow in rats.

Keywords: Nuclear factor kappa B; Corticotropin-releasing factor; Noradrenaline; Adrenaline; Inducible nitric oxide synthase; Plasma; Brain

1. Introduction

The transcription factor nuclear factor kappa B (NF-κB) is a complex nuclear DNA-binding protein whose activation triggers the transcription of a variety of specific target genes in many cells, including brain cells (Baeuerle, 1991; O'Neill and Kaltschmidt, 1997). NF-κB activity is attributed to the Rel/NF-κB family proteins forming homo- and heterodimers through the combination of the subunits p65 (or RelA), p50, p52, c-Rel and RelB. NF-κB is suppressed in the cytoplasm by a family of inhibitor molecules termed inhibitor kappa Bs, which bind NF-κB and mask its nuclear localization signal. When the inhibitor molecules are degraded, NF-κB migrates to the nucleus and activates the transcription of target genes (Ghosh et al., 1998; Pizzi and Spano, 2006).

It has been shown that activation of NF-κB is essential for expression of the inducible-type nitric oxide synthase (iNOS) gene (Xie et al., 1994; Aktan, 2004). Several studies indicate a close involvement of activation of NF-κB in the induction of gene expression of iNOS (Neufeld and Liu, 2003; Chun et al., 2004). In the nervous system, NF-κB is ubiquitously expressed by neurons, astrocytes, microglia and oligodendrocytes (Pizzi and Spano, 2006). Recent studies on NF-κB in the brain have shown that activation of NF-κB is involved in several pathological conditions to induce iNOS expression (Madrigal et al., 2001; Han et al., 2003; Zhao et al., 2007; Chan et al., 2007). These observations suggest that activation of NF-κB plays a pivotal role in transcription of the iNOS gene in the brain.

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Previously, we reported that intracerebroventricularly administered corticotropin-releasing factor (CRF) produced a gradual increase in plasma levels of noradrenaline and adrenaline in the brain cyclooxygenase-dependent manner via an activation of the CRF receptor $_1$ (Yokotani et al., 2001). In addition, the CRF-induced elevation of plasma catecholamines was dose-dependently attenuated by pretreatment with cycloheximide (an inhibitor of protein synthesis), N^{ω}-nitro-L-arginine methylester (a non-selective inhibitor of NOS), and S-methylisothiourea (an inhibitor of iNOS) (Okada et al., 2003). These results suggest the involvement of brain iNOS in the CRF-induced activation of central sympatho-adrenomedullary outflow in rats. Furthermore, several studies indicate the involvement of CRF in both the induction and binding activity of NF-κB in thymocytes (Smith et al., 2004; Zhao and Karalis, 2002). More recently, it has been demonstrated that CRF enhanced NF-κB-directed transcription in leukocytes by an activation of the CRF receptor $_1$ (Smith et al., 2006).

In the present experiments, therefore, we examined whether an activation of NF-κB is involved in the CRF-induced elevation of plasma catecholamines using urethane-anesthetized rats.

2. Materials and methods

2.1. Experimental procedures

Male Wistar rats weighing approximately 350 g were maintained in an air-conditioned room at 22–24 °C under a constant day–night rhythm for more than 2 weeks and given food (laboratory chow, CE-2; Clea Japan, Hamanatsu, Japan) and water ad libitum. Under urethane anesthesia (1.2 g/kg, intraperitoneally), the femoral vein was cannulated for infusion of saline (1.2 ml/h), and the femoral artery was cannulated for collecting blood samples. The animal was then placed in a stereotaxic apparatus, as shown in our previous paper (Okada et al., 2003). The skull was drilled for intracerebroventricular administration of test substances using a stainless-steel cannula (0.3 mm outer diameter). The stereotaxic coordinates of the tip of cannula were as follows (in mm): AP −0.8, L 1.5, V 4.0 (AP, anterior from the bregma; lateral from the midline; V, below the surface of the brain), according to the rat brain atlas of Paxinos and Watson (1997).

Three hours were allowed to elapse before the application of CRF or blocking reagents such as pyrrolidine dithiocarbamate ammonium salt (PDTC), SN50 with the amino acid sequence AAVALLPAVLLALLAPVQKLMP, SN50M as a corresponding cell-permeable inactive control scrambled peptide for SN50, and rosiglitazone. When the blocking reagents were used, CRF was administered intracerebroventricularly 60 min after the application of these blocking agents. CRF dissolved in sterile saline was injected slowly into the right lateral ventricle in a volume of 10 μl/animal using a 25-μl Hamilton syringe. PDTC, SN50, and SN50M dissolved in sterile saline were administered intracerebroventricularly in a volume of 5 μl/animal using a 10-μl Hamilton syringe. In case of rosiglitazone, the reagent was dissolved in 100% of *N,N*-dimethylformamide (DMF) and was administered intracerebroventricularly in a volume of 2.5 μl/animal using a 10-μl Hamilton syringe.

All experiments were conducted in compliance with the guiding principles for the care and use of laboratory animals approved by the Kochi University.

2.2. Measurement of plasma catecholamines

Blood samples (250 μl) were collected through an arterial catheter and were preserved on ice during the experiments. Plasma was prepared immediately after the final sampling. Catecholamines in the plasma were extracted by the method of Anton and Sayre (1962) with a slight modification, and were assayed electrochemically with high-performance liquid chromatography (Okada et al., 2003). Briefly, after centrifugation, the plasma (100 μl) was transferred to a centrifuge tube containing 30 mg of activated alumina (Wako pure chemical industries, Ltd., for catechol amine determination, acidic), 2 ml of double deionized water, 1 ml of 1.5 M Tris buffer (pH 8.6) containing 0.1 M disodium EDTA and 1 ng of 3,4-dihydroxybenzylamine as an internal standard. The tube was shaken for 10 min, and the alumina was washed three times with 4 ml of ice-cold double deionized water. Then, the catecholamines adsorbed onto the alumina were eluted with 300 μl of 4% acetic acid containing 0.1 mM disodium EDTA. A pump (EP-300: Eicom, Kyoto, Japan), a sample injector (Model-231XL: Gilson, Villiers-le-Bel, France) and an electrochemical detector (ECD-300: Eicom) equipped with a graphite electrode were used with high-performance liquid chromatography. Analytical conditions were as follows: detector, +450 mV potential against an Ag/AgCl reference electrode; column, Eicompack CA-50DS, 2.1×150 mm (Eicom); mobile phase, 0.1 M NaH_2PO_4–Na_2HPO_4 buffer (pH 6.0) containing 50 mg/l EDTA dihydrate, 0.75 g/l sodium 1-octanesulfonate and 15% methanol at a flow rate of 0.18 ml/min; injection volume, 40 μl. The amount of catecholamines in each sample was calculated using the peak height ratio relative to that of 3,4-dihydroxybenzylamine. By this assay, the intra- and inter-assay coefficients of variation were 3.0% and 3.7%, respectively, and 0.5 pg of noradrenaline and adrenaline were determined accurately.

2.3. Treatment of data and statistics

All values are expressed as the mean ± standard error of the mean. The data were analyzed by repeated-measures analysis of variance, followed by post hoc analysis with the Bonferroni method. *P* values less than 0.05 were taken to indicate statistical significance.

2.4. Compounds

The following drugs were used: synthetic CRF (rat/human) (Peptide Institute, Osaka, Japan); pyrrolidine dithiocarbamate ammonium salt (Sigma, St. Louis, MO, USA); activated alumina and SN50 (Wako pure chemical industries, Osaka, Japan); and SN50M (Calbiochem, La Jolla, CA, USA). rosiglitazone (Alexis, San Diego,CA, USA). All other reagents were the highest grade available (Nacalai Tesque, Kyoto, Japan).

3. Results

3.1. Effects of PDTC and SN50 on the CRF-induced elevation of plasma catecholamines

Vehicle-1 (5 μl saline/animal), vehicle-2 (10 μl saline/animal) and 7 instances of blood sampling over 6 h had no effect on the basal plasma levels of noradrenaline and adrenaline (Fig. 1, A and C). CRF administration (1.5 nmol/animal, intracerebroventricularly) elevated plasma levels of noradrenaline and adrenaline. These responses reached a maximun 120–180 min after administration, and the effects were prolonged throughout the experiments (Fig. 1, A and C).

Pretreatment with PDTC (9 nmol/animal, intracerebroventricularly) or SN50 (18 nmol/animal, intracerebroventricularly) had no effect on the plasma levels of catecholamines (Fig. 1, A and C). Pretreatment with PDTC attenuated the CRF-induced elevation of both noradrenaline and adrenaline in a dose-dependent manner (1 and 9 nmol/animal, intracerebroventricularly) (Fig. 1, A) (noradrenaline; at 180 min, F (2,19)=6.62, $P<0.025$, at 240 min, F (2,19)=3.15, $P<0.025$: adrenaline; at 60 min, F (2,19)=6.49, $P<0.025$, at 120 min, F (2,19)=6.31, $P<0.025$, at 180 min, F (2,19)=6.38, $P<0.025$, at 240 min, F (2,19)=9.91, $P<0.025$, at 300 min, F (2,19)=5.16, $P<0.025$, at 360 min, F (2,19)=3.74, $P<0.025$). When using the area-under-the-curve (AUC) to observe the effect of PDTC, the reagent (9 nmol/animal) significantly reduced the CRF-induced elevation of both plasma catecholamines (Fig. 1, B) (noradrenaline; F (2,19)=5.62, $P<0.025$: adrenaline; F (2,19)=5.93, $P<0.025$).

The CRF-induced elevation of both catecholamines was also attenuated by SN50, which is a well-defined, cell-permeable peptide that inhibits NF-κB translocation by competing with the NF-κB complexes, in a dose-dependent manner (9 and 18 nmol/animal, intracerebroventricularly), while SN50M, which is a corresponding cell-permeable inactive control scrambled peptide for SN50, was without effect on the CRF-induced elevation of both catecholamines (Fig. 1, C) (noradrenaline; at 120 min, F (2,14)=4.68, $P<0.025$, at 180 min, F (2,14)=6.62, $P<0.025$, at 300 min, F (2,14)=4.55, $P<0.025$: adrenaline; at 60 min, F (2,14)=6.80, $P<0.025$, at 120 min, F (2,14)=14.54, $P<0.025$, at 180 min, F (2,14)=10.41, $P<0.025$, at 240 min, F (2,14)=17.16, $P<0.025$, at 300 min, F (2,14)=8.51, $P<0.025$, at 360 min, F (2,14)=8.60, $P<0.025$). When using the AUC to observe the effect of SN50, the reagent significantly (18 nmol/animal) reduced the CRF-induced elevation of both plasma catecholamines (Fig. 1, D) (noradrenaline; F (2,14)=12.62, $P<0.025$: adrenaline; F (2,14)=14.55, $P<0.025$).

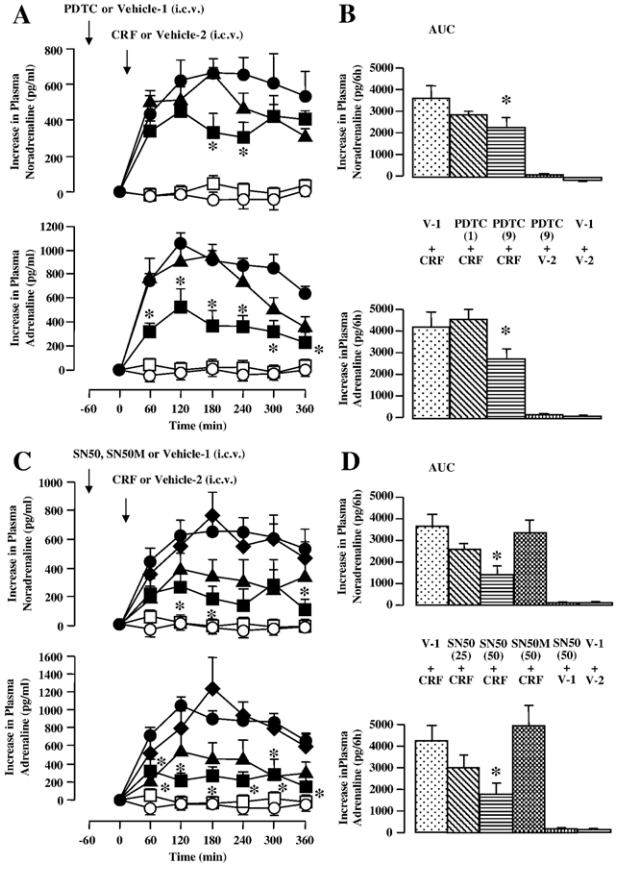

Fig. 1. Effect of PDTC and SN-50 on the CRF-induced elevation of plasma catecholamines. Increases in plasma noradrenaline (top panel) plasma adrenaline (bottom panel) above basal are shown (A and C). (A) PDTC (1.0 and 9.0 nmol/animal, intracerebroventricularly) or vehicle-1 (V-1) (saline 5 μl/animal) was administered intracerebroventricularly 60 min before the administration of CRF (1.5 nmol/animal, intracerebroventricularly) or vehicle-2 (V-2) (saline 10 μl/animal, intracerebroventricularly). Arrows indicate the i.c.v. administration of PDTC/vehicle-1 (V-1) and CRF/vehicle-2 (V-2). ○, V-1 plus V-2 (n=3); □, PDTC (9 nmol/animal) plus V-2 (n=4); ●, V-1 plus CRF (n=7); ▲, PDTC (1 nmol/animal) plus CRF (n=6); ■, PDTC (9 nmol/animal) plus CRF (n=9). Each point represents the mean±standard error of the mean. * $P<0.05$, significantly different from vehicle-1- and the CRF-treated group with the Bonferroni method. The actual values for noradrenaline and adrenaline at 0 min were 485.9±39.7 and 289.6±18.2 pg/ml in the vehicle-1-pretreated group (n=10), 405.8±41.9 and 173.7±16.8 pg/ml in the PDTC (1 nmol/animal)-pretreated group (n=6) and 620.8±63.5 and 468.3±48.1 pg/ml in the PDTC (9 nmol/animal)-pretreated group (n=13), respectively. (B) The area under the curve (AUC) of the CRF-induced elevation of plasma catecholamine levels above the basal in the presence or absence of PDTC is expressed as pg/6 h. (C) SN50 (9 and 18 nmol/animal, intracerebroventricularly) or SN50M (a cell permeable inactive control peptide of NF-κB) (19 nmol/animal, intracerebroventricularly) or vehicle-1 (V-1) (saline 5 μl/animal) was administered intracerebroventricularly 60 min before the administration of CRF (1.5 nmol/animal, intracerebroventricularly) or vehicle-2 (V-2) (saline 10 μl/animal, intracerebroventricularly). Arrows indicate the intracerebroventricular administration of SN50/SN50M/vehicle-1 (V-1) and CRF/vehicle-2 (V-2). ○, V-1 plus V-2 (n=3) (cited from A); □, SN50 (18 nmol/animal) plus V-2 (n=4); ●, V-1 plus CRF (n=7) (cited from A); ▲, SN50 (9 nmol/animal) plus CRF (n=4); ■, SN50 (18 nmol/animal) plus CRF (n=6), ♦, SN50M (19 nmol/animal) plus CRF (n=4). * $P<0.05$, significantly different from vehicle-1(V-1)- and the CRF-treated group with the Bonferroni method. Other conditions were the same as those of A. The actual values for noradrenaline and adrenaline at 0 min were 485.9±39.7 and 289.6±18.2 pg/ml in the vehicle-1-pretreated group (n=10) (cited from A), 380.7±45.2 and 219.6±58.2 pg/ml in the SN50 (9 nmol/animal)-pretreated group (n=4), 600.0±20.4 and 363.0±66.8 pg/ml in the SN50 (18 nmol/animal)-pretreated group (n=10) and 539.9±28.0 and 344.5±69.0 pg/ml in the SN50M (19 nmol/animal)-pretreated group (n=4), respectively. (D) The area under the curve (AUC) of the CRF-induced elevation of plasma catecholamine levels above the basal in the presence or absence of SN50 is expressed as pg/6 h.

3.2. Effects of rosiglitazone on the CRF-induced elevation of plasma catecholamines

Vehicle-1 (2.5 μl DMF/animal), vehicle-2 (10 μl saline/animal) and 7 instances of blood sampling over 6 h had no effect on the basal plasma levels of noradrenaline and adrenaline (Fig. 2A).Pretreatment with rosiglitazone (50 nmol/animal, intracerebroventricularly) had no effect on the plasma levels of catecholamines (Fig. 2A).

Pretreatment with rosiglitazone attenuated the CRF-induced elevation of both noradrenaline and adrenaline in a dose-dependent manner (25, 50 nmol/animal, intracerebroventricularly) (Fig. 2A) (noradrenaline; at 60 min, F (2,16)=4.95, P<0.025, at 180 min, F (2,16)=4.21, P<0.025, at 240 min, F (2,16)=7.53, P<0.025: adrenaline; at 180 min, F (2,16)=3.26, P<0.025, at 240 min, F (2,16)=3.93, P<0.025, at 300 min, F (2,16)=3.55, P<0.025, at 360 min, F (2,16)=3.57, P<0.025). When using the AUC to observe the effect of rosiglitasone, the reagent (50 nmol/animal) significantly reduced the CRF-induced elevation of both plasma catecholamines (Fig. 2B) (noradrenaline; F (2,16)=5.23, P<0.025: adrenaline; F (2,16)=4.12, P<0.025).

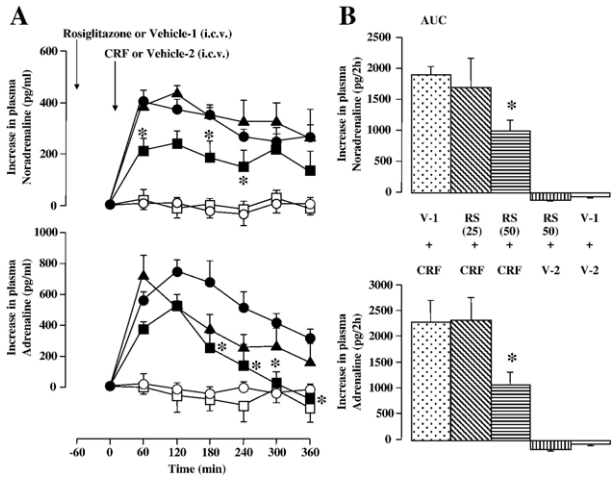

Fig. 2. Effect of rosiglitazone on the CRF-induced elevation of plasma catecholamines. (A) Rosiglitazone (RS) (25 and 50 nmol/animal, intracerebroventricularly) or vehicle-1 (V-1) (DMF 2.5 μl/animal) was administered intracerebroventricularly 60 min before the administration of CRF (1.5 nmol/animal, intracerebroventricularly) or vehicle-2 (V-2) (saline 10 μl/animal, intracerebroventricularly). Arrows indicate the i.c.v. administration of rosiglitazone/vehicle-1(V-1) and CRF/vehicle-2 (V-2). ○, V-1 plus V-2 (n=3); □, RS (50 nmol/animal) plus V-2 (n=4); ●, V-1 plus CRF (n=9); ▲, RS (25 nmol/animal) plus CRF (n=5); ■, RS (50 nmol/animal) plus CRF (n=5). Each point represents the mean±standard error of the mean. * P<0.05, significantly different from vehicle-1(V-1)- and the CRF-treated group with the Bonferroni method. The actual values for noradrenaline and adrenaline at 0 min were 155.3±11.9 and 161.8±32.1 pg/ml in the vehicle-1-pretreated group (n=12), 374.4±51.7 and 305.3±64.1 pg/ml in the rosiglitazone (25 nmol/animal)-pretreated group (n=5) and 307.8±62.1 and 248.1±56.1 pg/ml in the rosiglitazone (50 nmol/animal)-pretreated group (n=9), respectively. (B) The area under the curve (AUC) of the CRF-induced elevation of plasma catecholamine levels above the basal in the presence or absence of RS is expressed as pg/6 h. Other conditions are the same as those of Fig. 1.

4. Discussion

In the present study, the intracerebroventricularly administered CRF-induced elevation of plasma noradrenaline and adrenaline was dose-dependently attenuated by PDTC. PDTC is established as an inhibitor of NF-κB (Schreck et al., 1992; Liu et al., 1997; Nurmi et al., 2004; Zhou et al., 2007). Recent studies have indicated the inhibitory effect of PDTC on the increase in NF-κB-mediated iNOS expression in neurons, astroglia and gingivomucosal tissue (Madrigal et al., 2001; Marcus et al., 2003; Muia et al., 2006). Based on these observations and our previous report (Okada et al., 2003), it would be reasonable to assume that CRF induces iNOS expression via an activation of NF-κB and thereby elevates plasma catecholamines. However, PDTC is also known as an antioxidant (Sunderman, 1991; Bowie and O'Neill, 2000). In the next experiments, we examined the effect of SN50, a synthetic cell-permeable peptide that potently inhibits NF-κB translocation to the nucleus (Lin et al., 1995). Several studies have shown that this peptide effectively inhibits the activation of NF-κB by a variety of stimuli (Das et al., 2001; Liu et al., 2004; Lee and Rivier, 2005; Ramesh et al., 2007). In the present experiment, SN50 effectively reduced the CRF-induced elevation of both catecholamines. In contrast, SN50M, which is a corresponding cell-permeable inactive control scrambled peptide for SN50, had no effect on the CRF-induced responses. Although some studies have suggested that SN50 acts as a nonspecific inhibitor of NF-κB (Boothby, 2001), in light of the present study, it would be reasonable to assume that brain NF-κB plays a role in the CRF-induced central activation of sympatho-adrenomedullary outflow in rats.

The peroxisome proliferators-activated receptor-γ (PPARγ) agonist has been shown to down-regulate proinflammatory mediators mainly by inhibiting transcription of NF-κB-dependent inflammatory genes including iNOS gene (Collino et al., 2006; Colville-Nash et al., 1998; Daynes and Jones, 2002; Kielian and Drew, 2003). To further analyze a role for brain NF-κB in the CRF-induced elevation of plasma catecholamines, we examined the effect of rosiglitazone, which binds with the highest affinity to PPAR-γ of the PPAR-γ agonists tested to date (Lehmann et al., 1995). In the present experiment, the CRF-induced responses were also effectively attenuated by rosiglitazone. Although precise molecular mechanisms are still unknown, collectively, the present results might also support the idea that central NF-κB-mediated mechanisms play an important component of the CRF-induced central activation of sympato-adrenomedullary outflow in rats.

Although the NF-κB is diffusely expressed in the nervous system (O'Neill and Kaltschmidt, 1997), it is still obscure as to the brain sites for centrally administered CRF-induced activation of NF-κB. Recent reports have indicated the increased NF-κB p50 precursor p105 mRNA in the hypothalamic paraventricular nucleus in rats with heart failure (Yu et al., 2007) and the activation of NF-κB in the rostral ventrolateral medulla in mevinphos intoxication model of rat brain stem death (Chan et al., 2007). Interestingly, these brain regions are involved in central autonomic control (Swanson and Sawchenko, 1983;

Strack et al., 1989). To explore the brain sites responsible for activation of NF-κB is an intriguing question that should be clarified in further studies.

In the present experiments, we used anesthetized rats with very short post-surgery delay according to our previous reports (Yokotani et al., 2001; Okada et al., 2003). However, in this study, the possibility that the experimental conditions might influence the activation of NF-κB remains unresolved. Therefore, the data obtained in the present study would need to be interpreted cautiously when discussing their physiological significance.

In summary, we have demonstrated that brain NF-κB is involved in the CRF-induced sympatho-adrenomedullary outflow in rats.

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