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ORIGINAL ARTICLE

Hypoxia induces oxytocin release in the rat

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Abstract These studies were undertaken to investigate the impact of hypoxia on the release of oxytocin (OXT) at the median eminence (ME) in adult male rats, and the possible glucocorticoid involvement in modulating this release. Hypoxia was achieved in a hypobaric chamber. The results were as follows: (a) Acute hypoxic stress induced a release of OXT in ME proportional to its intensity and duration. (b) Chronic hypoxia (5–25 days) had no statistically significant influence on the ME level of OXT. (c) After bilateral adrenalectomy (ADX), the levels of OXT in ME were decreased, and there were no further significant changes in these levels when the rats were exposed to hypoxia. (d) The decrease of OXT in ME of ADX rats was partly reversed by replacement with dexamethasone (DEX, i.p. 500 μg/rat). These results suggest that acute hypoxia produces an intensity- and duration-dependent release of OXT and that such release may be modulated in part by hypoxia-activated high circulating glucocorticoids and their negative feedback on the release of corticotropin releasing hormone (CRH).

Introduction

It is considered that the essential function of oxytocin (OXT) is in parturition and lactation in female animals. However, recent evidence indicates that OXT release occurs in mammals, including humans, in response to various stress stimuli. OXT is produced in both females and males and the hypothalamic oxytocinergic neurons are distributed in a similar way in both sexes. Both osmotic and non-osmotic stressors induce OXT release. Possible function of stress-released OXT is not clear. A stimulatory role of OXT in the control of adrenocorticotropic hormone (ACTH) release was reported in the rat [1, 2]. OXT may mediate some immune and metabolic responses [3, 4], and also stimulate growth and have anti-stress [5] and behavioral effects and modulate memory processes [6].

Oxytocin release is increased in response to various types of stress such as restraint, immobilization, swimming, foot shock, cold, novel environment, ether and hypoglycemia [7–18]. Thus, novel environment stimuli in rats significantly increase plasma OXT concentrations. Intermittent foot shocks or conditioned fear stimuli facilite OXT secretion [19]. Likewise, stress due to shaking increases OXT content in the paraventricular nucleus (PVN) and plasma [20]. Forced swimming causes a significant rise in OXT release from both PVN and supraoptic nucleus (SON) [21]. Hypothalamic OXT release is accompanied by increased levels of this peptide in the systemic circulation [21]. Novelty and restraint stress increase OXT levels in the cerebrospinal fluid (CSF) of rats [22]. OXT release is stimulated after exposure to the stress-related behaviors of grooming, open field locomotion, and hot-plate analgesia. Restraint stress activates oxytocinergic c-fos expression of PVN neurons (22). Secretion of OXT from the posterior pituitary and ME is enhanced in response to insulin-induced hypoglycemia and other stimuli in human beings [23–25], but it is decreased during behavioral stress in nonhuman primates [26]. Overall, OXT secretion of ME does not appear to follow a common pattern for all stressors; rather, it shows wide variation depending on the nature of the stimulus.

The physiological significance of OXT release during stress is not clear; OXT increases in blood in response to stress and participates in the hypothalamo-pituitary-adrenocortical (HPA) activation by promoting ACTH release as induced by release of corticotropin-releasing hormone (CRH). OXT release may be involved in the regulation of ACTH secretion [1, 2].

Anatomically, there is a co-localization of OXT and CRH secreting cells in both parvicellular and magnocellular hypothalamic neurons [27, 28], and the PVN is essential for immobilization-induced OXT release. OXT cells in PVN might be the only ones involved in stress-induced OXT release [22]. OXT would exert a positive feedback on its own release. We have previously found that simulated altitude hypoxia can activate the HPA axis, markedly reduce CRH content in ME and hypothalamus, and cause increased plasma ACTH and corticosterone levels of rats [29–32].

Little is known of the possible effects of hypoxic stress on the OXT system. The present study was designed to explore (a) how a stress of simulated altitude hypoxia might influence OXT secretion at the ME and hypothalamus of rats, and (b) to investigate a possible correlation between OXT release and glucocorticoid levels during such hypoxic stress.

Materials and Methods

Animals.

Adult male Sprague-Dawley rats (150±20g) were used. They were maintained with a 12:12 h light/dark cycle (light on 07:00–19:00) and with free access to food and water. Animals were housed in groups of six and adapted to these conditions for one week prior to experimental manipulations.

Adrenalectomy (ADX) and sham operation were all performed under pentobarbital sodium anesthesia (Sigma, St. Louis. mo. 40 mg /kg i.p.). ADX was performed via a small incision in the ventral wall of the abdominal cavity; sham operations involved abdominal incision only. Dexamethasone (Sigma, 500 μg/rat) was given intraperitoneally (ip), 3 h before exposure to stress (6:00 a.m.). Controls received intraperitoneal injections of appropriate amounts of saline water. Sham-operated animals drank tap water; ADX rats received 0.9% NaCl in tap water. The experiment was performed in conscious rats, one week after ADX or sham operation.

Hypoxic stress (simulating altitude).

The rats were placed in a hypobaric chamber, the altitude was simulated at three levels of 0 km (sea level), 5 km (10.8% O_2, 54.02 KPA), 7 km (7.2% O_2, 41.04 KPA) for 30 minutes, 2h, 24h, and for a duration of 25 days, with the same conditions of light/dark cycle, nutrition and temperature described above.

Median eminence (ME) preparation.

After stress, the animals were decapitated between 09:00 and 11:00. The MEs were removed from the hypothalamus under a dissecting microscope and immediately stored at -80°C. They were later homogenized in glass homogenizers with 1.0

ml cold 0.1 NHCl. An aliquot (0.1 ml) was taken for the protein determination according to Lowry's method, and the remainders were centrifuged at 10,000g for 15 minutes at 4°C. Each supernatant (0.8 ml) was divided equally into two tubes, then lyophilized and stored at -80°C for OXT RIA. The extracted and lyophilized ME were reconstituted with 0.4 ml assay buffer.

Oxytocin (OXT) Assay.

OXT levels were measured by sensitive and specific RIA [33]. Oxytocin and antiserum were purchased from Peninsula Laboratory Inc. The intra-assay and inter-assay coefficient of variation were about 2.0% and 8.2%, respectively. All of the samples were measured concurrently to reduce experiment variation.

Statistics.

Data are expressed as mean ± S.D. and were analyzed statistically using a T-test and one-way anova. Significant differences were set at $P<0.05$.

Results

Acute hypoxia caused a decrease in ME content of OXT. As shown in Fig. 1.A and 1.B, exposure to hypoxia of 5 km (10.8% $O_{2)}$ and 7 km (7.2% $O_{2)}$ for 2 hrs decreased the OXT of ME from 132.33±33.52 (control group) to 113.83±59.9 ng/mg protein (not statistically different from controls) and to 33.6± 11.92 ng/mg protein ($p<0.001$). Hypoxic exposure of 5 km for 24 h resulted in a statistically significant decrease of OXT to 48.73±2 5.38 ng/mg protein ($P<0.001$).

Exposure to hypoxia of 5 km (10.8% $O_{2)}$ up to 25 days had no significant effect on the OXT levels of ME except for the first one day exposure which significantly reduced OXT content (Fig. 1.B and Fig. 2).

ADX induced a marked reduction of OXT content (68.72 ± 21.46 ng/mg protein) vs. control (132.33 ± 33.52 ng/mg protein ($P<0.01$). In the ADX rats, hypoxia at both altitudes had no further effects on OXT of ME (Fig. 3).

Administration of dexamethasone (i.p. 500 μg/rat) to ADX rats (with or without 0.9% NaCl in drinking water) induced a significant increase in OXT of ME after exposure to 5 km (10.8% O_2) altitude hypoxia for 2 h as compared to controls and sham-operated rats (Fig. 4).

Discussion

In recent years, much evidence demonstrates that OXT is released in response to various kinds of stress. The effects and regulatory mechanisms of acute and chronic hypoxia on OXT release have been

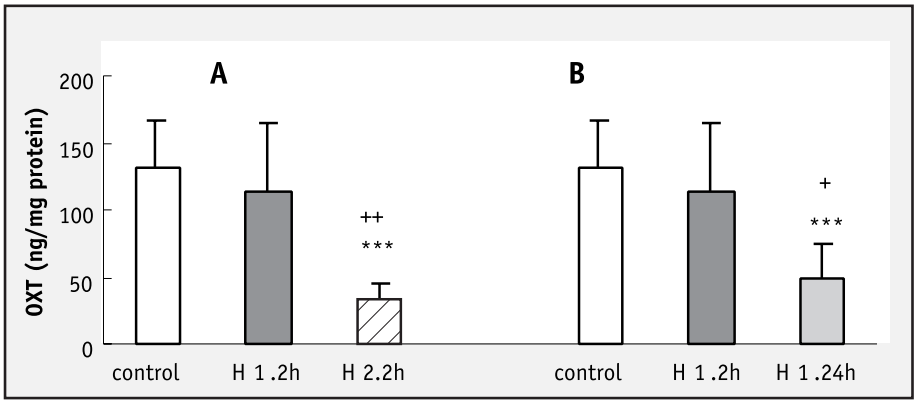

Fig. 1. Acute hypoxia reduces OXT content in ME of rats.

H1= 5 Km altitude, 10.8% $O_{2;}$
H2= 7 Km altitude, 7.2% $O_{2.}$
Barograms represent mean and the bracketed lines, the standard deviation (S.D.);
n (number of animals)=5–6;
+ P<0.05 H1.24h vs. control;
++ P<0.01 H2 vs. control;
*******P<0.001 H2.2h and H1.24 h vs. control

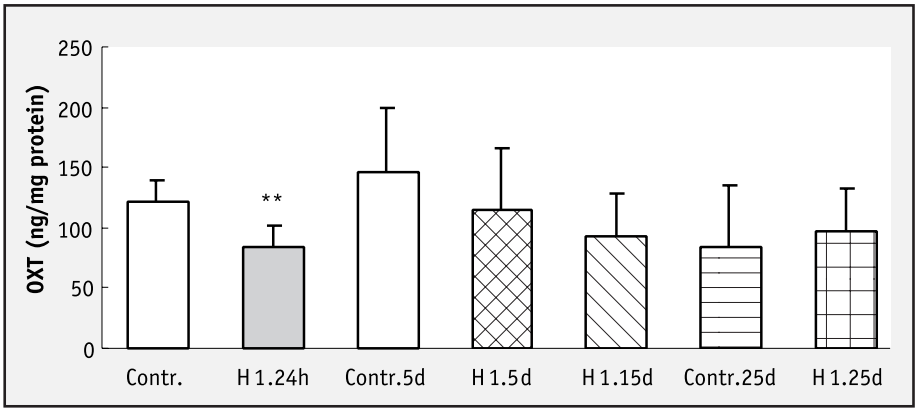

Fig. 2. Chronic hypoxia does not significantly influence OXT content in ME of rats.
Exposure to a high altitude of 5 km (10.8% O_2) lasted from 1–25 days.

All parameters presented are as in Fig. 1; **n**=4–6;
****** P<0.01 H1.24h vs. control.

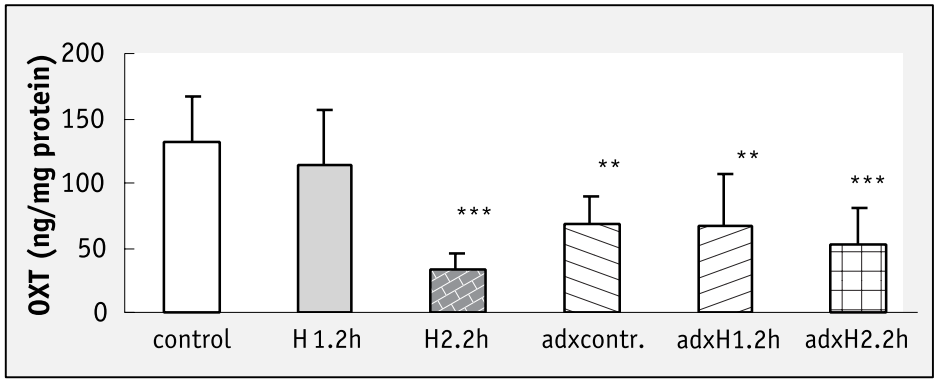

Fig. 3. Adrenalectomy reduces OXT content in ME of rats.

All parameters presented are as in Fig.1; **n**=5-6;
** P<0.01,
*** P<0.001 H1/H2 vs. intact control.

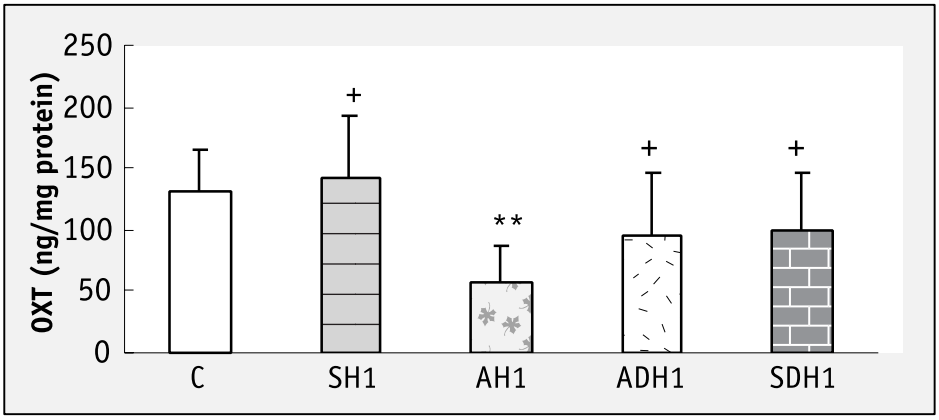

Fig. 4. Dexamethasone administration to ADX rats restores OXT content of ME reduced by ADX.

All parameters presented are as in Fig. 1;
n=5-6;
C=control; Sea level control;
SH1=shamADX+H1;
AH1=ADX+H1; ADH1=ADX+DEX+H1;
SDH1=shamADX+DEX+H1;
+ P<0.05 vs. ADX;
** P<0.01 vs. control.

poorly understood so far. The present study examined the influence of hypoxia on hypothalamic OXT release and hypothalamic content and possible mediation of HPA activation on the effects of hypoxia. The data presented here show that the hypoxia due to breathing 7.2% O_2 for 2 h or 10.8% O_2 for 24 h caused significant decreases in ME content of OXT compared to normal controls (Fig. 1.A and 1.B). Although these data suggest that decreased OXT content may be followed by an increased release and higher circulating blood levels, release and content of any given hormone may not always be reciprocally related. The moderate acute hypoxia at 5 km altitude for 2 h did not cause a significant reduction of OXT levels in ME; that is, it did not stimulate OXT release at ME terminals into hypophyseal portal blood. However, the severe acute hypoxia at 7 km altitude even for 2 h could promote OXT release as suggested by the significantly reduced OXT content of ME. Chronic exposure to moderate hypoxia (5 km,10.8% O_2) induced a significant reduction in OXT content after one day exposure but OXT content returned to normal values as the exposure was prolonged to 25 days. Thus, the influence of simulated altitude hypoxia on OXT release in ME of the hypothalamus of rats may be correlated with hypoxia severity and time-course.

Earlier experiments had shown that stresses other than hypoxia caused release of hypothalamic OXT. Thus, shaker stress in rats induced a significant OXT decrease in hypothalamic PVN and an increase in peripheral blood concentration [9]. Forced swimming caused a significant rise in OXT within both the SON (3-fold over control) and PVN (4-5-fold over control) [10]. In rats, a novel environment, immobilization and ether inhalation induced a significant increase in OXT levels in the cerebrospinal fluid, and immobilization and ether stress induced a rapid increase in plasma OXT level [18]. OXT contents of ME decreased after frustration stress [34]. In contrast, the contents of OXT within PVN and ME determined by quantitative immunohistochemistry were unchanged after long-term social isolation stress [35]. When axonal transport was blocked by colchicine, ME content of OXT remained unchanged after hypoglycemia, novelty and restraint stress [36].

The mechanism of the OXT release induced by hypoxia is unclear. We propose that the HPA axis, activated by hypoxia, might be involved in OXT release. We have previously documented that rats made hypoxic by simulated altitude of 5 km (10.8% 0_2) and 7 km (7.2% O_2) for various intervals of time had activated HPA axis, as manifested by acutely and subacutely increasing CRH release from ME, enhanced plasma ACTH and corticosterone, and increased expression of CRH mRNA in PVN determined by *in situ* immunocytochemistry (29–32). This

activated HPA axis might act on the OXT release. Reciprocally, a stimulatory role of OXT in the control of ACTH release in the rat has also been suggested [1, 2]. Co-localization of CRH and OXT neurons has been documented [27, 28]. CRH is known to induce OXT release [37, 38]. We propose that hypoxia-activated CRH acts directly on OXT release. There is evidence that OXT exerts a positive feedback function on its own release [39]. Also, it has been reported that OXT mediates lymphokine production [3]. We have previously demonstrated that the hypoxia-induced inhibition of immune function, both cellular and humoral, resulted from an increased CRH secretion [40–42]. In addition, OXT has a role of anti-stress in the clinic [5]. Therefore, it is reasonable to postulate that hypoxia-induced OXT release has important physiological significance in inhibiting immune function during hypoxia.

In a number of studies, it has been reported that after ADX of rats, the OXT content of ME increased, decreased, or showed no changes [43, 44]. The present data show that after bilateral ADX, the OXT content in rat ME dramatically decreased ($p<0.01$ vs. control, $p<0.05$ vs. shamADX) (Fig. 3) . The partial reversal of this OXT decrease by dexamethasone replacement (Fig. 4) suggests that hypoxia-stress-stimulated OXT secretion from ME and increased circulatory glucocorticoid might play a negative feedback role in OXT release at ME. When ADX rats were treated with dexamethasone and further exposed to hypoxia, OXT levels were no further decreased but rather showed some recovery towards levels resembling those of intact animals. While OXT content decreased in the ME of ADX rats, substantial and sustained increase occurred in plasma OXT concentrations in these animals [45]. It appears that circulating glucocorticoids might exert a tonic inhibitory effect on the release of OXT in response to peripheral stimulation by Interleukin-1β. Osmotic stimulation of ADX rats by hypertonic saline markedly diminishes OXT content in the inner layer of the ME [46] and OXT receptor binding is increased by stress in areas of the CNS that are rich in glucocorticoid receptors [47].

Direct synaptic contacts of nor-epinephrine (NE) axon terminals with both CRH and OXT neurons in the PVN have been demonstrated. There is evidence that expression of α_{1D}-adrenergic receptor mRNA in OXT- and CRH-synthesizing neurons occurs in the rat PVN [48]. The facilitating effects of norepinephrine in stress-activated-HPA axis directly affect CRH- or OXT-synthesizing neurons. Thus, hypoxia-induced NE release may act through hypoxia-activated-CRH release and consequently the increased circulating glucocorticoid levels may be involved through their negative feedback on CRH.

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REFERENCES

1 Gibbs DM. Immunoneutralization of oxytocin attenuates stress-induced corticotrophin secretion in the rat. Regul Pept 1985; **12**:273–277.
2 Gibbs DM. Vasopression and oxytocin: hypothalamic modulators of the stress response: a review. Psychoneuroendocrinology 1986; **11**:131–140.
3 Johnson HM, Torres BA. Regulation of lymphokine production by arginine vasopressin and oxytocin: modulation of lymphocyte function by neurohypophyseal hormones. J Immunol 1985; **135**: 773–775.
4 Whittio PD, Rodrigues LM, Hems DA. Stimulation by vasopressin, angiotensin and oxytocin of gluconeogenesis in hepatocyte suspensions. Biochem J 1978; **176**:893–898.
5 Uvnaes-Moberg K. Oxytocin linked antistress effects- the relaxation and growth response. Acta Anaesthesiol Scand 1997; **161**: Suppl 640.
6 Richard P, Moos F, Freund-Mercier MJ. Central effects of oxytocin. Physiol Rev 1991; **71**:331–370.
7 Lang RF, Heil JWE, Ganten D, Hermann K, Unger T, Rascher W. Oxytocin unlike vasopression is a stress hormone in the rat. Neuroendocrinology 1983; **37**:314–316.
8 Gibbs DM. Dissociation of oxytocin, vasopressin and corticotropin secretion during different types of stress. Life Sci 1984; **35**: 487–491.
9 Carter DA, Lightman SL. Diurnal pattern of stress-evoked neurohypophyseal hormone secretion: sexual dimorphism in rats. Neurosci Lett 1986; **71**:252–255.
10 Hashimoto K, Murakami K, Takao T, Makino S, Suagawara M, Ota Z. Effect of acute ether or restraint stress on plasma corticotropin releasing hormone, vasopressin and oxytocin levels in the rat. Acta Med Okayama 1989; **43**:161–167.
11 Ivanyi T, Wiegant VM, de Wied D. Differential effects of emotional and physical stress on the central and peripheral secretion of neurohypophysial hormones in male rats. Life Sci 1991; **48**:1309–1316.
12 Crine AF, Buijs RM. Electric footshocks differentially affect plasma and spinal cord vasopressin and oxytocin levels. Peptides 1987; **8**:243–246.
13 Higuchi T, Honda K, Negoro H. Influence of oestrogen and noradrenergic afferent neurons on the response of LH and oxytocin to immobilization stress. J Endocrinol 1986; **110**:245–250.
14 Higuchi T, Honda K, Takano S, Negoro H. Stress-induced oxytocin release in the rat after lesion of the paraventricular nuclei: possible deficiency of corticotropin releasing factor. J Neuroendocrinol 1990; **2**:647–651.
15 Bjorkstrand E, Eriksson M, Uvnas-Moberg K. Plasma levels of oxytocin after food deprivation and hypoglycaemia, and effects of 1-deamino-2-D-Tyr-(Oet)-4-Tyr-8-Orn-oxytocin on blood glucose in rats. Acta Physiol Scand 1992; **144**:355–359.

16 Jezova D, Michajlovskij N, Kvetnansky R, Makara GB. Paraventricular and suppraoptic nuclei of the hypothalamus are not equally important for oxytocin release during stress. Neuroendocrinology 1993; **57**:776–781.
17 Romero LM, Plotsky PM, Sapolsky RM. Patterns of adrenocorticotropin secretagog release with hypoglycemia, novelty, and restraint after colchicine blockade of axonal transport. Endocrinology 1993; **132**:199–204.
18 Jezova D, Skultetyova I, Tokarevvv DI, Bakoss P, Vigas M. Vaspressin and oxytocin in stress. Ann NY Acad Sci 1995; **77**: 192–203.
19 Onaka T, Palmer JR, Yagi K. Norepinephrine depletion impairs neuroendocrine responses to fear but not novel enviromental stimuli in the rat. Brain Res 1996; **713**:260–268.
20 Nishioka T, Anselmo-Franci JA, Li P, Callahan M, Morris M. Stress increases oxytocin release within the hypothalamic paraventricular nucleus. Brain Res 1998; **781**:57–61.
21 Wotjaak CT, Ganster J, Kohl G, Holsboer F, Landgraf R, Engelmann M. Dissociate central and peripheral release of vasopressin, but not oxytocin. in response to repeated swim stress: New insights into the secretory capacities of peptidergic neurons. Neuroscience 1998; **85**:1209–1222.
22 Miyata S, Itoh T, Lin SH, Ishiyama M, Nakashima T, Kiyohara T. Temporal changes of c-fos expression in oxytocinergic magnocellular neuroendocrine cells of the rat hypothalamus with restraint stress. Brain Res Bull 1995; **37**:391–395.
23 Fisher BM, Baylis PH, Frier BM. Plasma oxytocin, arginine vasopressin and atrial natriuretic peptide responses to insulin-induced hypoglycemia in man. Clin Endocrinol (Oxf) 1987; **26**: 179–185.
24 Nussey SS, Page SR, Ang VTY, Jenkins JS. The response of plasma oxytocin to surgical stress. Clin Endocrinol (Oxf) 1988; **28**:277–282.
25 Chiodera P, Volpi R, Gaiazza A, Davoli C, Marchesi C, Papadia C, et al. Inhibitory effect of dexamethasone on the oxytocin response to insulin-induced hypoglycemia in normal men. J Endocrinol Invest 1992; **15**:459–463.
26 Kalin NH, Gibbs DM, Barksdale CM, Shelton SE, Carnes M. Behavioral stress decreases plasma oxytocin concentrations in primates. Life Sci 1985; **36**:1275–1280.
27 Dohanics J, Kovacs KJ, Makara GB. Oxytocinergic neurons in rat hypothalamus. Neuroendocrinology 1990 **51**:515–522.
28 Sawchenko PE, Swanson LW, Vale W. Corticotropin releasing factor coexpression within distinct subsets of oxytocin, vasopressin and neurotensin immunoreactive neurons in the hypothalamus of the male rat. J Neurosci 1984; **4**:1118–1129.
29 Du JZ (author), Ohno H, et al. (editors). The brain CRF during hypoxia in: Progress in Mountain Medicine and High Altitude Physiology, Press Committee of the 3rd World Congress on Mountain Medicine and Altitude Physiology. Matsumoto. Japan. 1998. p. 416–417.
30 Du JZ, You ZB. A radioimmunoassay of corticotropin releasing factor of hypothalamus in *ochotona curzoniae*. Acta Theriologica Sinica 1992; **12**:223–229.
31 Du JZ, Wu Y, Kuang X. Second messengers mediate CRF releasing under simulated hypoxia. Chinese J Appl Physiol 1998 **14**: 198–200.
32 Yang SM, Du JZ, Li LC. Effect of hypoxia on the development of hypothalamic corticotropin-releasing factor of neonatal rats. Chinese J Appl Physiol 1996; **12**:294–297.
33 Vecaernyes M, Torok A, JoJart I, Laczi F, Penke B, Julesz J. Specific radioimmunoassay of oxytocin in rat plasma. Endocr. Regul. 1994; **28**:145–150.
34 Romero L II, Levine S, Sapolsky R II. Adrenocorticotropin secretagog release: stimulation by frustration and paradoxically by reward presentation. Brain Res 1995; **676**:151–156.
35 Sachez II, Aguado F, Scachez-Toscano F, Saphier D. Neuroendocrine and immunocytochemical demonstrations of decreased hypothalamo-pituitary-adrenal axis responsiveness to restraint stress after long-term social isolation. Endocrinology 1998; **139**:579–587.
36 Romero L, Plotsky P, Sapolsky R. Patterns of adrenocorticotropin secretagog release with hypoglycemia, novelty, and restraint after colchicine blockade of axonal transport. Endocrinology 1993; **132**:199–204.
37 Higuchi T, Honda K, Takano S, Negoro H. Stress-induced oxytocin release in the rat after lesion of the paraventricular nuclei; possible deficiency of corticotrophin releasing factor. J Neuroendocrinol 1990; **2**:647–651.
38 Bruhn TO, Sutton SW, Plotsky PM, Vale WW. Central administration of corticotropin-releasing factor modulates oxytocin secretion in the rat. Endocrinology 1986; **119**:1558–1563.
39 Moos F, Freund-Mercier MJ, Guerne Y, Gueme JM, Stoeclel ME, Richard P. Release of oxytocin and vasopressin by magnocellular nuclei in vitro: specific facilitatory effect of oxytocin on its own release. J Endocrinol 1984; **102**:63–72.
40 Bai HB, Du JZ, Jia HW. Inhibition effect of hypoxia on humoral immunity of rats. Acta Physiologica Sinica 1997 **49**:167–172.
41 Bai HB, Du JZ. Corticotropin-releasing factor mediates lymphocyte proliferation suppression induced by hypoxia stress. Chinese J Appl Physiol 1995; **11**:201–204.
42 Verbalis JG, Baldwin EF, Ronnekleiv OK, Robinson AG. In vitro release of vasopressin and oxytocin from rat median eminence tissue. Neuroendocrinology 1986; **42**:481–8.
43 Spinedi E, Giacomini M, Jacquier MC, Gaillard RC. Changes in the hypothalamo-corticotropic axis after bilateral adrenalectomy: evidence for a median eminence site of glucocorticoid action. Neuroendocrinology 1991; **53**:160–170.
44 Harbuz MS, Chover-Gonzalez AJ, Conde GL, Renshaw D, Lightman SL, Jessop DS. Interleukin-1 β-induced effects on plasma oxytocin and arginine vasopressin: role of adrenal ster-oids and route of administration. Neuroimmunomodulation 1996; **3**:358–63.
45 Mink D, Lang RE, Ostermann E, Bock R. Effect of salt loading and salt deprivation on the vasopressin and oxytocin content of the median eminence and the neural lobe in adrenalectomized rats. Cell Tissue Res 1986; **24**:413–23.
46 Liberzon I, Young EA. Effects of stress and glucoco ticoids on CNS oxytocin receptor binding. Psychoneuroendocrinology 1997; **22**:411–422.
47 Bai HB, Du JZ. Norephinephrine regulation of T-lymphocyte proliferation of rat during acute hypoxia. Acta Physiologica Sinica 1997; **49**:261–266.
48 Sands SA, Morii DA. Expression of a_{1D}adrenergic receptor messenger RNA in oxytocin- and corticotropin-releasing hormone-synthesizing neurons in the rat paraventricular nucleus. Neuroscience 1999; **91**:639–649.