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Cervical sympathectomy affects adrenocorticotropic hormone and thyroid-stimulating hormone in rats

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Abstract: To examine the effects of bilateral cervical sympathectomy on the secretion of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), and prolactin (PRL), 18 male rats were divided into three groups: control (Cont), sham operation (Sham), and bilateral cervical sympathectomy (Symp). All rats were kept under a normal circadian rhythm for 2 weeks. Subsequently, blood was collected and plasma ACTH as well as serum TSH, GH, and PRL levels were measured. The difference in ACTH levels between the Cont and Sham groups was not significant, but ACTH levels in the Symp group were significantly higher than those in the other groups. The difference in TSH levels between the Cont and Sham groups was also not significant, but TSH levels in the Symp group were significantly lower than those in the Cont group. There were no statistically significant differences in GH and PRL levels among these groups. The present results suggest that cervical sympathectomy in the rat increases ACTH secretion and decreases TSH secretion in the pituitary. These effects seem to be due to a mildly increased secretion of melatonin in the pineal body that probably in turn increases corticotropin-releasing factor (CRF) secretion and decreases thyrotropin-releasing hormone (TRH) secretion in the hypothalamus. Extrapolation of these findings to humans suggests that long-term and repeated stellate ganglion block would affect the pituitary secretions of ACTH and TSH.

Key words: Cervical sympathectomy, Stellate ganglion block, Adrenocorticotropic hormone, Thyroid-stimulating hormone, Growth hormone, Prolactin, Rat

Introduction

Cervical sympathectomy in the rat has been regarded as one of the experimental models that could reveal the mechanism of stellate ganglion block for humans. Using this male model, we [1] documented that bilateral cervical sympathectomy normalizes gonadotropin secretions under continuous exposure to light, and we considered this mechanism to act by affecting the circadian rhythm of melatonin in the pineal body. Melatonin may also affect corticotropin-releasing factor (CRF) and thyrotropin-releasing hormone (TRH), among others, in the hypothalamus [2,3]. The present study was designed to examine the effects of cervical sympathectomy on adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), and prolactin (PRL) levels in rats.

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Materials and methods

Eighteen adult male Wistar rats weighing 255.3 ± 15.5 g (mean ± SD) were used, and this study was conducted in accordance with the Fukushima Medical College Guidelines on Animal Experiments, the Japanese Animal Protection and Management Law (No. 105), and the Japanese Regulations on the Feeding and Safekeeping of Animals (No. 6).

The rats were randomly divided into three groups of six rats each: control (Cont), sham operation (Sham), and bilateral cervical sympathectomy (Symp) groups. Cervical sympathectomy and sham operation were performed with the animals under pentobarbital 50 mg·kg^{-1} i.p. and atropine sulfate 0.05 mg·kg^{-1} i.m. The superior cervical ganglia were exposed through a ventral incision in the neck, and both inferior extremities of the ganglia were cut off in the Symp group. In the Sham group, only the bilateral superior cervical ganglia and sympathetic trunks were exposed. The Cont group did not undergo surgery. After these procedures, all rats were given access to food and water ad libitum, and kept under a normal circadian rythm consisting of a 12-h light-dark cycle at a room temperature of 24°C for 2 weeks.

On the last day, blood was collected from the animals' hearts, with all rats under pentobarbital 50 mg·kg^{-1} i.p. The blood samples were immediately centrifuged at 1000 g for 15 min, and the serum and plasma were separated. Plasma ACTH, and serum TSH, GH, and PRL levels were assayed by radioimmunoassay. The ACTH assay kit was provided by Nippon DPC (ACTH 24 Kit, Chiba, Japan), and the TSH, GH, and PRL assay kits were obtained from Amersham (Rat TSH Assay System, Rat GH Assay System, and Rat PRL Assay System, respectively, Buckinghamshire, UK).

Data are presented as the mean ± SD. The results were statistically analyzed by one-way analysis of variance (ANOVA, Fisher PLSD, Stat View SE+, Abacus Concepts, Berkeley, CA, USA), and $P < 0.05$ was taken as the level of significance.

Results

In all rats, the operation and anesthesia were performed without complications. Bilateral palpebral ptosis and retraction were observed in the Symp group during the 2-week study period.

The plasma ACTH levels were 303.0 ± 61.1 pg·ml^{-1}, 226.0 ± 50.8 pg·ml^{-1}, and 464.8 ± 120.3 pg·ml^{-1} in the Cont, Sham, and Symp groups, respectively. The difference between the Cont and Sham groups was not significant, but ACTH levels in the Symp group were significantly higher than those in the other groups. The serum TSH levels were 5.6 ± 2.35 ng·ml^{-1}, 4.5 ± 0.96 ng·ml^{-1}, and 3.2 ± 1.19 ng·ml^{-1} in the Cont, Sham, and Symp groups, respectively. The difference between the Cont and Sham groups was not significant, but TSH levels in the Symp group were significantly lower than those in the Cont group (Fig. 1).

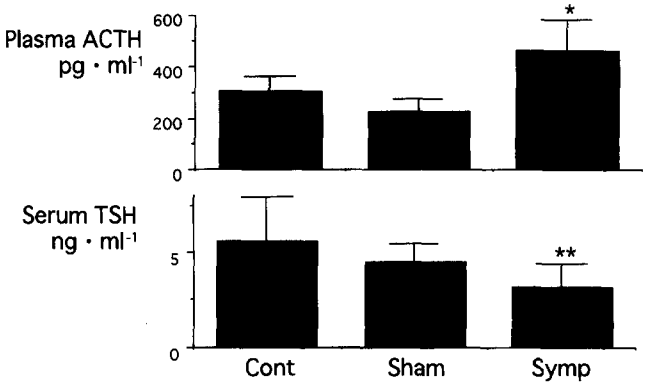

Fig. 1. Plasma adrenocorticotropic hormone (*ACTH*) and serum thyroid-stimulating hormone (*TSH*) levels of each group. There were no significant differences between the control (*Cont*) and sham operation (*Sham*) groups. ACTH levels in the bilateral cervical sympathectomy (*Symp*) group were significantly higher than those in the other groups. TSH levels in the Symp group were significantly lower than those in the Cont group. Values are the mean ± SD n = 6. *$P < 0.01$ vs Cont or Sham; **$P < 0.05$ vs Cont

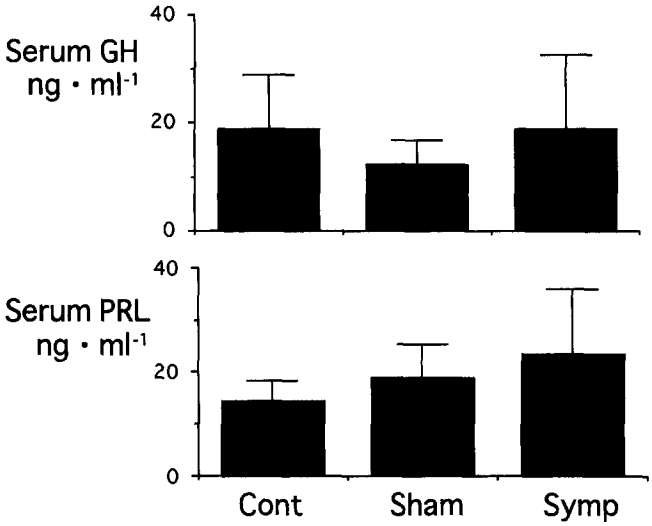

Fig. 2. Serum growth hormone (*GH*) and prolactin (*PRL*) levels in each group. There were no statistically significant differences among these groups. Values are the mean ± SD, $n = 6$

The serum GH levels were 18.9 ± 9.86 ng·ml^{-1}, 12.5 ± 4.30 ng·ml^{-1}, and 18.8 ± 13.90 ng·ml^{-1} in the Cont, Sham, and Symp groups, respectively. There were no statistically significant differences among these groups. The serum PRL levels were 14.5 ± 3.90 ng·ml^{-1}, 18.9 ± 6.30 ng·ml^{-1}, and 23.4 ± 12.50 ng·ml^{-1} in the Cont, Sham, and Symp groups, respectively. There were also no statistically significant differences among these groups (Fig. 2).

Discussion

The present study revealed that bilateral cervical sympathectomy increases ACTH, decreases TSH, and does not affect GH or PRL levels in male rats during the first 2 weeks after surgery. These results imply that cervical sympathectomy may affect CRF and TRH secretions in the hypothalamus. To explain the mechanism of these results, the cervical sympathetic nervous system and the circadian secretion of melatonin in the pineal body should first be discussed.

The cervical sympathetic nerve is one of the autonomic nervous systems in which light-induced stimulation reaches the pineal body, thereby regulating melatonin secretion [4,5]. Thus, in the daytime there is little secretion of melatonin, and it increases remarkably at night. Continuous exposure to light completely abolishes the distinct circadian rhythm of melatonin secretion; however, continuous darkness maintains this

rhythm in a relatively stable manner, and melatonin stays mildly elevated [6]. According to this paper [6], bilateral cervical sympathectomy seems to resemble being placed in a continually dark environment, and probably increases melatonin secretion slightly.

There are no previous reports about the relationship between CRF or TRH secretion and cervical sympathectomy except for superior cervical ganglionectomy (SCGx). Romeo et al. [7] examined ACTH levels during sympathetic nerve degeneration following SCGx of rats, and documented a significant rise of ACTH until 54 h postoperatively; these levels returned to the preoperative values by 120 h later. Cardinali et al. [8] demonstrated that SCGx in the rat increased the TRH content of the median basal hypothalamus until 24 h postoperatively; these values returned to the preoperative levels 72 h later, suggesting a transient depression of TRH and TSH secretions. The mechanism of ACTH increase and TSH decrease is due to a transient increase of norepinephrine (NE) release from the sympathetic nerve terminals in the median eminence undergoing wallerian degeneration at the early phase after SCGx, followed by increasing CRF and decreasing TRH secretions. After this period, the NE release seems to fall and be gradually exhausted. Thus, ACTH and TSH also change transiently and return to the preoperative levels gradually. Unlike SCGx, cervical sympathectomy in the present model does not seem to cause wallerian degeneration because cutting off both inferior extremitties of the superior cervical ganglia does not traumatize the ganglia. Therefore, the function of the median eminence may be kept within normal limits, and the hypothalamic hormonal secretions may not be affected by the median eminence. Cervical sympathectomy probably affects only the pineal body by cutting off the sympathetic nerve input of light stimulation, thereby simulating continuous darkness, followed by a mild rise of melatonin secretion. If melatonin secretion increases CRF and decreases TRH secretions in the hypothalamus, the present results, i.e., the ACTH increase and the TSH decrease, can be explained.

The circadian rhythm of ACTH in humans shows high values in the morning and low values at night, which are widely recognized as constituting the distinct circadian rhythm. That in the rat, however, has been reported to be the complete inverse of the human rhythm, probably because the rat is a nocturnal animal [9,10]. Therefore, the hypothesis that cervical sympathectomy simulates a continually dark environment does not contradict the present results with regard to ACTH. As to the circadian rhythm of rat TSH, it is still unknown. However, since human TSH reaches peak levels at midnight, it is quite probable that rat TSH might show peak levels in the daytime. These speculations would also not contradict the present results regarding TSH.

Little has been reported about the relationship between GH or PRL secretion and the cervical sympathetic nerve. SCGx in the rat decreases serum GH and PRL levels until 24 h postoperatively; they return to the preoperative values 72 h later [8]. These changes seem to resemble those seen in the TRH levels; however, in the present study, serum GH and PRL levels after cervical sympathectomy showed no significant changes. GH or PRL secretion from the pituitary seems to be regulated in a complicated manner by certain hypothalamic hormones. Thus it is difficult to explain the effects of cervical sympathectomy on GH or PRL secretion in the present result.

In conclusion, the present study in the rat demonstrates that bilateral cervical sympathectomy increases plasma ACTH levels, decreases serum TSH levels, and does not affect serum GH and PRL levels. The mechanism of these changes seems to act by a mild increase in melatonin secretion in the pineal body that probably increases CRF and decreases TRH secretions in the hypothalamus. Extrapolation of these findings to humans suggests that long-term and repeated stellate ganglion block would affect the pituitary secretions of ACTH and TSH.

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