EXPERIMENTAL BIOLOGY

Sex-Dependent Peculiarities in the Brain Stem-Regulated Corticosterone Secretion in Rats

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Iontophoretic administration of 6-hydroxydopamine into the area where catecholaminergic neurons of the dorsal vagal complex (A2 group) are located and loading with glucose induce sex-dependent differences in the corticosterone secretion in rats.

Key Words: *sexual dimorphism; catecholaminergic neurons; corticosterone*

In our previous investigation demonstrating the involvement of the dorsal vagal complex (DVC) neurons in the regulation of carbohydrate homeostasis [1], it was noted that some of these neurons display sexual dimorphism [2]. Based on this finding, we hypothesized that DVC neurons participate in the realization of sex-dependent variations of carbohydrate homeostasis.

In the present study, special attention is paid to the histophysiology of group A2 catecholaminergic (CA) DVC neurons [4]. These cells are involved in the realization of cardiovascular, digestive, and respiratory reflexes and play an important role in the maintenance of energy homeostasis [3-5]. Recently, it has been found that group A2 neurons participate in the innervation of the hypothalamic paraventricular nucleus neurons synthesizing corticotropin-releasing factor (CRF) [7,8]. Since CRF acts as a factor triggering universal adaptive responses, for example, stress reactions, it can be suggested that CA neurons of the DVC are involved in the initiation of stress reactions in response to various homeostatic disorders. This study is an attempt to evaluate the role of group A2 CA neurons in stress reactions and to find out to what extent the histophysiological responses of these neurons are sex-dependent.

To this end, male and female rats were loaded with glucose to impair homeostasis after selective destruction of group A2 CA neurons with the specific neurotoxin 6-hydroxydopamine.

MATERIALS AND METHODS

Thirty male and thirty-two female Wistar rats weighing 180-200 g were used. In the experimental group (16 males and 16 females), 6-hydroxydopamine was introduced iontophoretically into the caudal area of the DVC as defined with the use of a stereotaxic atlas [6]. Sham-operated rats (control) were subjected to the same manipulations without neurotoxin. Some rats in both groups were loaded with glucose (40% solution instead of water). After 4 weeks, the rats were decapitated, the medulla oblongata was removed to confirm morphologically that the neurotoxin was introduced into the appropriate locus, and blood was collected for radioimmunoassay to determine the corticosterone content with standard Steron-K-I-125 kits. Radioactivity was measured in an automatic Mini Gamma counter. The concentrations of the studied hormones were calculated from radiometric data using a Data Box microprocessor.

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TABLE 1. Blood Corticosterone Levels (nmol/liter) Before and After Administration of 6-Hydroxydopamine and on Days 14 and 28 of Maintenance on Glucose-Rich Diet

Duration of glucose loading	Sex	Sham-operated rats	Rats given 6-hydroxydopamine	Sham-operated rats loaded with glucose	Rats given 6-hydroxydopamine and loaded with glucose
14 days	Males	118.4±13.4	158.4±17.2*	168.2±17.2	221.9±21.5***
	Females	130.2±12.8	145.2±18.3	152.2±16.5	167.1±17.3
28 days	Males	120.9±18.8	91.2±4.3	87.1±8.7	94.4±8.3
	Females	134.0±15.7	182.4±13.1*	46.5±9.1	223.6±57.1*

Note. *$p<0.01$: compared with sham-operated rats; $p<0.001$: **compared with rats given 6-hydroxydopamine; *compared with sham-operated rats loaded with glucose.

RESULTS

Administration of 6-hydroxydopamine into the DVC area and subsequent maintenance of rats on a carbohydrate-rich diet led to considerable changes in the blood corticosterone content. It should be noted that these changes were sex-dependent (Table 1).

An acute response to glucose load was observed in male rats with destroyed group A2 CA neurons during the first half of experimental period. Their blood corticosterone levels were significantly ($p<0.001$) higher than in sham-operated animals receiving the same diet. Blood corticosterone concentration was increased in 6-hydroxydopamine-treated rats without subsequent glucose loading, remaining lower than in rats given a 40% glucose solution instead of water.

After 14 days of glucose loading, the response to 6-hydroxydopamine was less pronounced in females than in males. Although blood corticosterone levels in these females were higher than in sham-operated females, the differences were insignificant. Blood corticosterone content was higher in glucose-loaded females with damaged group A2 neurons than in females maintained on a normal diet, the difference being also insignificant.

After 28 days of glucose loading, blood corticosterone content was almost normal in experimental and sham-operated males, while in glucose-loaded females it was significantly ($p<0.001$) higher than in sham-operated females and 6-hydroxydopamine-treated males.

Slight changes in blood corticosterone content were observed in 6-hydroxydopamine-treated females which were not loaded with glucose.

Our results show that group A2 CA neurons are involved in the regulation of corticosterone secretion which is controlled by sex-dependent mechanisms. The response of the hypothalamic-pituitary-adrenal system to chemical destruction of group A2 neurons manifests itself as a significantly increased blood corticosterone content in glucose-loaded animals. This increase suggests that at least one component of central mechanisms responsible for an adequate response to changes in carbohydrate metabolism is "switched off" when the CA innervation of CRF-secreting hypothalamic neurons is interrupted. Moreover, the alterations in blood corticosterone content were sex-dependent; 28 days after destruction of DVC neurons, blood levels of immunoreactive corticosterone in glucose-loaded female rats were significantly higher than in males. From these findings it can be concluded that the mechanisms underlying the catecholaminergic control of CRF-secreting hypothalamic neurons by the brain stem are sex-dependent.

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