Abstract of Doctoral Thesis

Roles of estrogen in regulation of the psychological stress-induced cardiovascular responses in rats

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School of Natural Science and Ecological Awareness,
Graduate School of Humanities and Sciences, Nara Women's University
Shoko Tazumi

ABSTRACT

The psychological stress is recognized as a major risk factor in the development of cardiovascular diseases, including hypertension, coronary artery disease, and arrythmia. In women, menopause is also a well-known risk factor of the cardiovascular disease. Our previous study revealed that estrogen suppressed the stress-induced cardiovascular responses in the ovariectomized rats, but the mechanisms accounting for the inhibitory effect of estrogen remained unclear. In this study, we examined the mechanism by which estrogen replacement attenuates pressor and tachycardiac responses to psychological stress using the ovariectomized female rats. Ovariectomized rats were randomly assigned to be implanted subcutaneously with 17β-estradiol or placebo, and the rats underwent cage-switch stress. The blood pressure (BP) and the heart rate (HR) were measured using telemetry system in freely moving rats. This thesis consists of three chapters.

In chapter 1, we investigated whether estrogen suppressed the stress-induced pressor response via renin-angiotensin system (RAS). As is well known, the RAS plays an important role in regulating BP and body fluid volume. The RAS activity is enhanced during the stress responses to physiological/psychological stressors. However, there are no study has shown whether estrogen attenuates the psychological stress-induced activation of RAS. In this study, we used losartan, an angiotensin II (Ang II) type 1 receptor blocker, to study the contribution of Ang II in stress-induced pressor response. Consistent with our previous reports, the cage-switch stress-induced pressor response was suppressed by estrogen. And then, the losartan revealed the possible contribution of estrogen on suppressing stress-induced pressor response via Ang II. Moreover, estrogen

suppressed the stress-induced elevation of plasma renin activity and Ang II concentration in ovariectomized rats. These results suggest that the inhibitory effects of estrogen on psychological stress-induced activation of the RAS could be at least partially responsible for the suppression of the pressor responses to psychological stress.

In chapter 2, we investigated whether estrogen replacement attenuates stress-induced pressor responses due to vasorelaxation via β_2-AR in ovariectomized rats. Psychological stress activates the sympathetic nervous system, which causes the release of norepinephrine from nerve endings and epinephrine from an adrenal gland. They activate both α_1-adrenoceptors (AR) in vessels and β_1-AR in the heart, resulting in hypertension or tachycardia. Thus, ARs are important regulators of cardiovascular physiology. In this study, we investigated the possibility that estrogen suppressed stress-induced BP response due to vasorelaxation via β_2-AR induced by sympathetic nervous system hyperactivity in peripheral blood vessels during stress. The results suggested that β_2-AR is involved in the inhibitory effects of estrogen, because butoxamine, a β_2-AR blocker, enhanced the stress-induced BP response only in the estrogen-treated ovariectomized rats. In addition, estrogen enhanced the β_2-AR related depressor response and vasorelaxation response. The over-expression of β_2-AR mRNA in resistance arteries explains at least partially why estrogen treatment suppressed vasoconstriction during stress.

In chapter 3, we investigated the effects of estrogen on suppressing the stress-induced tachycardia. Psychological stress activates the sympathetic nervous system, and one important target of adrenergic stimulation is the heart, where activation of β-AR induces increases in heart rate, relaxation speed and contractility. Reactive oxygen species (ROS) are also associated with various types of stresses, and recent studies reported a relationship between β-adrenergic system and ROS production in vessel. This study was undertaken to elucidate whether chronic estrogen replacement attenuates psychological stress-induced tachycardiac responses by suppressing β_1-AR and its cell signaling related to NADPH oxidase-derived ROS production in ovariectomized rats. From our results, it is considered that inhibitory effects of estrogen on the stress-induced HR response were related to β_1-AR and NADPH oxidase. In addition, estrogen downregulated the expression of β_1-AR mRNA and protein

expression in heart, suggesting the roles of estrogen in regulation of the stress-induced tachycardia in ovariectomized rats.

In conclusion, estrogen suppressed the circulating RAS activation and the vasoconstriction in peripheral arteries caused by psychological stress, resulting in suppressed stress-induced pressor response in ovariectomized rats. Moreover, estrogen attenuates the stress-induced tachycardiac responses by suppressing β_1-AR and NADPH oxidase-derived ROS production in ovariectomized rats. We demonstrated, for the first time to our knowledge, that estrogen suppressed the stress-induced cardiovascular responses by regulating the circulating RAS and β-AR expression in peripheral arteries and heart.