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Changes in cardiovascular function based on adrenalin and norepinephrine metabolism in ovariectomized rats

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ABSTRACT

Menopause is a cardiovascular risk factor in women, and cardiovascular changes during perimenopause can increase the risk. We observed the influence of plasma adrenalin and norepinephrine and their metabolites on the cardiovascular system and the rectification effect of estrogen in ovariectomized rats. Fifty-four adult female Sprague-Dawley rats were randomly divided into sham (Sham), ovariectomized (OVX), or ovariectomized + estrogen treatment groups (OVX + E), with 18 rats in each. The Sham and OVX groups were given normal saline and the OVX + E group was given estradiol valerate beginning 2 weeks after ovariectomy and continuing for 4 weeks. Radioimmunoassay, high-performance liquid chromatography, high-performance liquid chromatography-tandem mass spectrometry, and chromatography-spectrophotometry were used to detect estradiol, adrenalin, norepinephrine, metanephrine, and normetanephrine in plasma and vanillylmandelic acid in urine. Echocardiography, Doppler blood flow detection technologyand hamnatodynamometer were applied to assess cardiovascular function. After ovariectomy, levels of estrogen reduced, adrenalin and metanephrine increased, and norepinephrine and normetanephrine in the plasma and vanillylmandelic acid in urine decreased. Symptoms indicative of cardiac diastolic dysfunction, including decreased diastolic left ventricular cavity capacity, increased wall thickness and decreased cardiac rate were observed. Different degrees of vasomotor dysfunction appeared in different peripheral positions, and the tail vessels were in relatively systolic conditions. However, the claw pad vessels were diastolic. Besides, blood pressure also increased. After ovariectomy, estrogen levels reduced and the metabolic processes of adrenalin and norepinephrine changed, which impacted cardiovascular functions. Changes of adrenalin and norepinephrine and its metabolites were correlated with the cardiovascular function. Cardiovascular disease occurred during the perimenopausal period. Estrogen replacement therapy can mitigate, rectify, and improve menopause-related conditions such as hot flash.

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1. Introduction

Menopause is considered to be a cardiovascular risk factor in women. The prevalence of cardiovascular disease increases four-fold after the age of 50 (Yang et al., 2012). Compared to nonmenopausal women of the same age, menopausal women have an approximately 2.5 times higher risk of cardiovascular disease (Knowlton and Lee, 2012; Murphy, 2011), which is believed to be due to the decline in estrogen level caused by increased age and ovarian failure, leading to a decrease in the cardioprotective effect of estrogen (Lisabeth et al., 2009).

Estrogen is a fat-soluble steroid hormone, which diffuses into target tissue through blood circulation. Estrogen has several target tissues; it plays an important role not only in regulation of the genital system, but also in prophylaxis for cardiovascular disease (Burns and Korach, 2012; Rosano et al., 2012). When the estrogen level in perimenopausal women decreases and autonomic nerve dysfunction occurs, the cardiac autonomic nervous system and the regulatory effect of angiocarpy may both dysfunction, and cardiovascular system symptoms such as hot flash, hypertension, and coronary heart disease occur. Freedman (2005) suggests that adrenalin and norepinephrine are related to the occurrence of cardiovascular symptoms in the perimenopausal period and that estrogen has a regulatory effect on the concentration of adrenalin and norepinephrine (Romanovsky et al., 2009). Adrenalin and norepinephrine are important factors in the occurrence and development of cardiovascular disease, and may cause some diseases that are mainly

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characterized by hypertension and hypermetabolism due to the disorder (Rossouw et al., 2002). Some clinical and animal experiments also show that estrogen can regulate the activity of the cardiovascular system by altering the activity of the sympathetic nerves (Kawano et al., 2003).

The structural and functional status of the heart and blood pressure can change during the perimenopausal period. With the decline in estradiol level and varying degree of damage of the cardiac systolic and diastolic functions, some cardiac function impairments such as increase of the left ventricular septal and posterior wall thickness and decrease in cardiac motion speed during the systolic and diastolic periods are seen in perimenopausal women, but left ventricular ejection fraction does not significantly change (Düzenli et al., 2007). One study showed that estradiol can cause peripheral vasodilatation, increase coronary blood supply, and have a protective effect on the cardiovascular system (Mumford et al., 2011). Its mechanism is realized by β1-AR and β2-AR (Wu et al., 2008), which prompt the adrenergic pathway and may play an important role in the regulation of cardiac function during the perimenopausal period.

It is well known that epinephrine can speed up cardiac rate (positive, chronotropic effect), strengthen systolic function (positive, inotropic effect), speed up atrioventricular junctional conduction (positive, dromotropic effect), and improve cardiac diastolic function (relaxation effect). Epinephrine can also lead to arrhythmia, cardiac hypertrophy, and other adverse effects. The effect adrenalin plays on the heart is mainly realized by its combination with β-adrenergic receptors (Parati and Esler, 2012), and it has a positive inotropic effect (Heubach et al., 2003), mainly through β1-AR coupling excitability G (Gαs) protein. Climacteric women may have a change not only in cardiac function but also in hypertension, which increases more rapidly than in men of similar age (Coylewright et al., 2008; Reckelhoff and Maric, 2010). This difference may result from estrogen's effects on the cardiovascular system. Studies have shown that estradiol can regulate blood pressure by regulating the expression and distribution of its receptor and the function of vascular endothelial cells (Gupte et al., 2012).

At the same time, with the onset of hypertension, the reduction of aorta elasticity can further augment pulse pressure and left ventricular load, which cause left ventricular hypertrophy, reduce coronary perfusion, and form a vicious circle over time. Langrish et al. (2009) reported that natural 17β-estradiol can significantly lower the blood pressure of patients with premature ovary failure. Recently, a 10-year cross-sectional survey showed that postmenopausal women who take long-term combined estrogen have a lower hypertension incidence and diastolic blood pressure than those who do not, but there was no significant difference in systolic blood pressure (Fung et al., 2011). Thus, the authors speculated that the changes in cardiac structure, function and blood pressure may result from the changes of adrenalin and its receptor under low estrogen during the perimenopausal period.

Another change in the cardiovascular system during the perimenopausal period is vasomotor function disorder, with hot flash as a representative symptom (Low et al., 2008). Hot flash is a strong feeling with hectic symptoms in the skin of the head, face, neck, and chest, accompanying some autonomic nerve disorder symptoms such as perspiration, palpitation, anxiety, and irritability, which may be more prominent at night (Woods and Mitchell, 2010). About 75% of patients with perimenopausal syndrome may have hot flashes (Tuomikoski et al., 2011). Many studies have found that perimenopausal women who experienced hot flash are more prone to cardiovascular disease during the postmenopausal period. Furthermore, for those with vascular symptoms such as hot flash, the incidence of cardiovascular disease will increase significantly in the postmenopausal period (Szmuilowicz et al., 2011). The peripheral mechanism of hot flash is still unclear, but it is known that norepinephrine mainly regulates vasomotor function, and hot flash results from vasomotor function disorder. It can therefore be inferred that norepinephrine plays an important role in the occurrence of hot flash during the perimenopausal period. A randomized controlled trial suggests that perimenopausal women's hot flashes relate to arterial diastolic function, which may have potential effects on cardiovascular disease (Tuomikoski et al., 2009).

When hot flash occurs, the sympathetic nervous system (especially the skin) activity strengthens, and skin blood flow increases (Low et al., 2011). Animal experiments show that estrogen level fluctuation causes changes in norepinephrine during the perimenopausal period, and when hot flash occurs, brain norepinephrine neurotransmitters increase, which influences temperature adjustment function (Albertazzi, 2006). However, peripheral vascular contraction mainly comes from the vasoconstrictor sympathetic nerve of thoracolumbar spinal fracture, which receives signals from the centrum. Norepinephrine released by neurotransmitter endings makes the vessel contract through its effect on vascular smooth muscle. In general, the most intense form of vascular contraction caused by sympathetic activities appears in the skin. Some studies show that hot flash is closely related to vascular endothelial dysfunction (Thurston et al., 2008; Gerber et al., 2007). The concentration of norepinephrine varies inversely with endothelial-dependent vasodilator function (Kaplon et al., 2011a). As women grow older, estrogen levels reduce and the viscosity of norepinephrine increases, which influence endothelium-dependent vasodilatation function and finally lead to vasomotor dysfunction, which causes hot flash. At the same time, a clinical study shows that the use of norepinephrine as a re-intake inhibitor can significantly improve perimenopausal hot flash (Umland and Falconieri, 2012). Thus, vasomotor dysfunction may have a close relation with norepinephrine when estrogen levels decrease during the perimenopausal period.

After exerting corresponding effectiveness in cardiovascular system, adrenalin and norepinephrine in blood are changed into metanephrine (MN) and normetanephrine (NMN) by catechol-*O*-methyltransferase (COMT) (Eisenhofer et al., 1995). Compared with adrenalin and norepinephrine, MN and NMN can rapidly reflect their long-term secretion and are not influenced by short-term secretion (Lenders et al., 2002). In addition, the half-life of plasma MN and NMN is longer than that of the prototype and does not easily fluctuate (Hoizey et al., 2002). Finally, MN and NMN convert to vanillylmandelic acid (VMA) by means of a series of enzymatic reactions and then eject from urine (Eisenhofer et al., 2001). The change of the metabolic process of adrenalin and norepinephrine has significant meaning for the study of the change of cardiovascular function after estrogen levels reduce. When the estrogen level is low, expression of ester biosynthesis-related genes of adrenalin and norepinephrine is in dispute (Sabban et al., 2010). So far, there has not been a study on the relation between the change of adrenalin and norepinephrine in peripheral blood and the change of cardiovascular function during the perimenopausal period.

Thus, this study aims to discuss the relationship between some concerning symptoms and the functions of the cardiovascular system and norepinephrine metabolism in the perimenopausal period, and probe into whether estrogen replacement therapy can rectify that process or not.

2. Materials and methods

2.1. Drugs

Estradiol valerate was manufactured by the Guangdong Branch of Bayer Healthcare Co, Ltd., China (Bujiale®, 1 mg/tablet). Estradiol valerate tablets were suspended in normal saline via sonication, and the homogeneous suspensions were maintained by stirring. The concentration of the estradiol was 0.2 mg/mL.

2.2. Animals and treatments

Fifty-four healthy female Sprague-Dawley rats aged 8 to 10 weeks and weighing 220 ± 10 g were purchased from the Department of Laboratory Animals of Peking University Health Science Center. The

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