Autonomic regulation of cardiovascular function: influence of sex hormones and environmental nano-contaminants

PHAM THUY LINH

With more than a quarter of hypertensive patients resistant to existing anti-hypertensive therapy, hypertension is a significant public health challenge worldwide. More performant anti-hypertensive drugs are necessary but their development implies a better understanding of molecular mechanisms leading to high blood pressure. It is well described that essential hypertension is correlated with a high sympathetic nerve activity (SNA). Several brain cardiovascular centers (BCCs) located in the brain stem, hypothalamus, and limbic system modulate blood pressure levels by controlling the SNA in both physiological and pathological conditions. The central regulation of cardiovascular function involves complex mechanisms influenced by multiple genetic, hormonal, and environmental factors.

The amygdala is a brain area of the limbic system in charge of mediating autonomic responses to stress and regulating negative emotion in the brain of humans, rats, and other mammals. It has neural connections with other BCCs such as nucleus tractus solitarii (NTS), a key region for regulating the set point of blood pressure. Amygdala expresses high estrogen receptor levels and is involved in the control of behavioral and hormonal responses to stress or fear. It is believed that hormonal shift (estrogen deficit) after menopause contributes to women's hypertension and changes in the control of their emotions. Besides, it is reported that the injection of estrogen receptor agonist in medial amygdala prevents stress-induced elevation of blood pressure in ovariectomized rats. However, the involvement of sex hormones in these mechanisms and the neurohormonal mechanisms involved in the changes in blood pressure control are poorly understood. We hypothesized that high estrogen levels contribute to premenopausal characteristics by activating specific genes and pathways of the amygdala involved in the mechanisms regulating basal blood pressure level, motivation, and body weight. We tested the effect of one-month estradiol treatment on the gene expression profile of amygdala in ovariectomized young adult female spontaneously hypertensive rats. Estradiol substitution significantly decreased blood pressure, prevented body weight gain, and increased the voluntary physical activity of ovariectomized rats. In parallel, estradiol treatment downregulated the expression of genes associated with "estrogen signaling pathway," "cholinergic synapse," "dopaminergic synapse," and "long term depression" pathways in the amygdala of ovariectomized rats. These results suggest that the amygdala may be involved in estrogen-dependent regulation of blood pressure, body weight control, and behavior in young adult female spontaneously hypertensive rats and provide a deeper understanding of the underlying mechanisms through which estrogen protects premenopausal women from post-menopausal symptoms.

The central nervous system is sensitive to sex hormones and is also vulnerable to nano-pollutants. Accumulating evidence shows that nanoplastics (NPs) pollutants may be harmful to the central nervous system to organisms exposed to them on a long term. The potential hazard of the tiniest NPs originates from their capacity to cross biological membranes, be up-taken by cells, and alter their function. According to recent findings, ingested NPs can cross intestinal barriers, travel in the bloodstream, and accumulate in various tissue. Moreover, chronic oral exposure to NPs was shown to induce behavior alteration in rats and reduce locomotor activity in marine species at the early development stage, suggesting that they reach the CNS and alter its functions. NPs are believed to cross blood-brain barriers, and at the cellular level, NPs were shown to trigger neurotoxicity, inflammatory, oxidative stress, and apoptotic response, and be internalized by microglia. However, very little is known about the impact of NPs on neural tissue *in vivo*, and to our knowledge, virtually no studies are focusing on the effects of NPs on blood-brain barrier-free regions of the central nervous system, such as

circumventricular areas (CVOs). The **area postrema (AP)**, one of the CVOs, is a paired structure located in the medulla oblongata of the brainstem and involved in body fluid homeostasis and blood pressure (**BP**) control via its connection with the NTS and other autonomic control centers in brainstem. Assuming that chronic oral exposure of rats to NPs results in a constant level of circulating NPs, we hypothesized that NPs interact with AP and alter its molecular characteristics and autonomic function through microglia activation. We investigated whether the chronic oral exposure of rats to NPs is associated with **(1)** an alteration of their physiological and biological parameters, **(2)** an alteration of the morphology of their microglia in AP **(3)** a change in AP gene expression profile. Our data show that daily oral exposure of Wistar rats to NPs for two months significantly decreased their heart rate and increased their urine osmolality without affecting their body weight, food and water uptake, and urine volume. These results suggest that mechanisms involved in vagal reflex and osmoregulation are affected by NPs in rats. Moreover, microglial cells in the AP were found more reactive in the brain of rats exposed to NPs than that of control rats. These observations suggest that AP microglia may be sensitive to circulating NPs and mediate changes in the function of surrounding neurons, which could affect the mechanisms involved in the regulation of heart rate and urine osmolality regulation. Those data are, to our knowledge, the first ones to demonstrate that the regular oral intake of NPs may impact the molecular characteristics and autonomic function of blood-brain barrier-free areas of the brain.