Iran J Public Health, Vol. 51, No.10, Oct 2022, pp.2372-2374

Letter to the Editor

Effects of Menopause on Physical Activity and Dopamine Signaling in Women

Dong-Il Kim [1,2], ****Young-Min Park*** [1,3]

1. *Division of Health and Kinesiology, Incheon National University, Incheon, Republic of Korea*
2. *Sports Functional Disability Institute, Incheon National University, Incheon, Republic of Korea*
3. *Sport Science Institute & Health Promotion Center, Incheon National University, Incheon, Republic of Korea*

***Corresponding Author:** Email: ypark@inu.ac.kr

(Received 05 Apr 2022; accepted 19 Apr 2022)

Dear Editor-in-Chief

Physical Activity in Menopausal Women

More than 60% of women fail to engage in the U.S. guidelines of physical activity and a positive correlation has been found between physical inactivity and mortality in women. Women 60 yr of age and older show a greater prevalence of physical inactivity (1). Pre-clinical studies with ovariectomized rodents suggest that a lack of ovarian hormones reduces physical activity levels. A human longitudinal study (2) also demonstrated that women exhibited a significant reduction in physical activity 2 yr before menopause and remained reduced. This physical inactivity is associated with decreased circulating estrogen levels during the menopausal transition. These preclinical and clinical studies strongly suggested the existence of a significant physiological factor during menopause, and estrogen has been believed the main controller involved in menopause-related behavioral changes.

Brain Dopamine Signaling and Physical Activity

Mesolimbic dopamine circuits in the brain play a critical role in the regulation of motivation, motor control, and reward, which can significantly contribute to voluntary physical activity. Among the circuits, the dopamine system in the nucleus accumbens (NAc) seems to be a major controller for voluntary physical activity (3). There are two types of dopamine receptors in dopamine neurons, the D1-like receptor (stimulatory receptors, D1 and 5) containing no introns and the D2-like receptor (inhibitory receptors, D2, 3, and 4) containing introns acting through Gi-proteins (4). In a preclinical study, injecting a D1 receptor agonist into the NAc increases physical activity, while a D1 receptor antagonist decreases it (5). These findings confirmed the significant role of dopamine activity in voluntary physical activity.

Estrogenic activation is the critical link for physical activity, and estrogen modulates neurotransmitters including dopamine (6). Menopause-related deficiency in estrogen decreases voluntary physical activity along with attenuated dopamine activity (7). Estrogen appears to exert a tonic stimulation for dopamine receptors and in turn maintain overall dopamine activity, which positive stimulation is attenuated after menopause in women or ovariectomized rodents. However, estrogen replacement therapy immediately after

ovariectomy conserved the upregulated D1-like dopamine receptors (8).

Our group previously determined the potential role of NAc dopamine activity in voluntary wheel running in female rats (9). Using rats selectively bred for high (HCR) and low (LCR) aerobic capacity showing a divergence in wheel running behavior, we found that HCR rats had greater wheel running distance and the activation of dopamine signaling compared to LCR rats. HCR rats had greater D1 stimulatory receptors and lower D3 & 4 inhibitory receptor mRNA expressions compared to LCR rats. However, ovariectomy significantly up-regulated inhibitory dopamine receptors (i.e. D2 and 4 receptor mRNA expressions) in HCR rats, implying a strong effect of menopause independent of one's aerobic capacity. All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Missouri-Columbia.

Estrogen Receptor (ER) α Signaling and Physical Activity

ERα signaling is an obligatory mediator for the ovariectomy-mediated reduction in voluntary physical activity. Using genetically knock-out (KO) mice, Ogawa et al (10) initially demonstrated that ERα signaling appears more likely involved in enhanced spontaneous physical activity in ovariectomized mice, rather than ERβ-pathway. This group showed that estrogen administration increased spontaneous physical activity only in ERβ KO mice but failed in ERα KO mice. This strongly supports the hypothesis that the estrogenic increase in spontaneous physical activity is primarily mediated by the ERα-signaling pathway. To our knowledge, none of the previous studies investigated the effect of ERα signaling on dopamine receptors and voluntary running activity. Future studies should further investigate the specific mechanisms by which estrogen and its receptors (ERα and β) regulate brain dopamine metabolism in menopausal women.

Acknowledgements

This research was supported by the Incheon National University (2019-0367).

Conflict of interest

The authors declare that there is no conflict of interest.

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