EXERCISE SCIENCE 운동과학
Vol.32, No. 1, February 2023: 3-10
https://doi.org/10.15857/ksep.2023.32.1.3
ISSN(Print) : 1226-1726
ISSN(Online) : 2384-0544
REVIEW ARTICLE

Menopause Induces Physical Inactivity through Brain Estrogen Receptor and Dopamine Signaling

Nyeonju Kang[1,2,3,†] **PhD, Dong-Il Kim**[4,5,†] **PhD, Young-Min Park**[3,4] **PhD**

[1]Division of Sport Science & Sport Science Institute, Incheon National University, Incheon; [2]Neuromechanical Rehabilitation Research Laboratory, Incheon National University, Incheon; [3]Sport Science Institute & Health Promotion Center, Incheon National University, Incheon; [4]Division of Health and Kinesiology, Incheon National University, Incheon; [5]Sports Functional Disability Institute, Incheon National University, Incheon, Korea

PURPOSE: Genes had selectively evolved to enhance the motivation for physical movement in human during the Paleolithic era. To prepare for a potential forthcoming food deficiency, high physical activity was essential for survival in the environment where hunting wild animals and gathering plants. In modern society, however, developing technology and engineering has made human life easier to accomplish tasks with not much movement and effort, resulting in a profound deficiency in physical activity (i.e., physical inactivity).

METHODS: In this review, the authors summarized previous studies searched by the PubMed, Google Scholar, and Science Direct databases.

RESULTS: Reduced physical activity is significantly associated with the high prevalence of various diseases including metabolic syndrome, obesity, sarcopenia, and cancer. Unfortunately, in women, menopause negatively impacts their body and physiology mainly due to the loss of estrogens, which also contributes to behavioral changes such as a significant reduction of physical activity levels during menopausal transition. In this review, the author focused to describe the underlying brain mechanism by which menopause results in reduced levels of physical activity through estrogens, estrogen receptors, and dopamine signaling in the nucleus accumbens, the main controller for exercise motivation.

CONCLUSIONS: Estrogen receptor, specifically ERα, and dopamine receptors are the main controllers for voluntary physical activity. Furthermore, high running motivation is associated with enhanced dopamine activity. More studies are needed to verify whether enhanced dopamine activity can protect against menopause-associated reduction in physical activity.

Key words: Menopause, Physical Inactivity, Dopamine, Exercise Motivation, Estrogen Receptor

INTRODUCTION – MENOPAUSE AND METABOLIC SYNDROME

Menopause, defined as no continuous menstruation for 12 months, significantly contributes to metabolic syndrome [1]. The period of irregular menstrual cycle is called the menopausal transition [2], and one of the biggest physiological changes is a rapid decrease in circulating estrogen levels. A sharp decrease in estrogen exacerbates many of the clinical risk factors contributing to metabolic syndrome and imposing physiological stress during menopause [3].

The prevalence of metabolic syndrome varies in women, ranging from 14% to 60% in premenopausal and postmenopausal women, respectively [4,5]. Research demonstrated that, compared to premenopausal women, postmenopausal women had a higher prevalence of metabolic syndrome [6]. Metabolic syndrome is represented by several features including dyslipidemia, insulin resistance, the accumulation of abdominal visceral adiposity, hypertriglyceridemia, and low levels of low-density lipoprotein [7]. Metabolic syndrome appears to be a public health issue

Corresponding author: Young-Min Park **Tel** +82-32-835-8586 **Fax** +82-32-835-0788 **E-mail** ypark@inu.ac.kr
*This research was supported by the Incheon National University (2021-0202).
†These authors contributed equally to the manuscript as first author.
Received 7 Feb 2023 **Revised** 23 Feb 2023 **Accepted** 27 Feb 2023

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2023 Korean Society of Exercise Physiology

due to its contribution to major diseases such as stroke, non-alcoholic steatohepatitis, ischemic heart disease, dementia, endometrial cancers, and polycystic ovarian disease [8]. Given that life expectancy is greater than 80 years these days, women after menopause should live for more than 30 years. To improve the quality of later life of women, this public issue needs to be thoroughly examined by manifesting the underpinning mechanisms by which menopause contributes to metabolic syndrome. Sarcopenia has been believed one of the major factors increasing the prevalence of metabolic syndrome.

METHODS

In this review, the authors collected and summarized previous studies searched by the PubMed, Google Scholar, and Science Direct databases. The searching keywords were 'menopause and physical activity level', 'physical inactivity and dopamine', 'menopause and exercise motivation', 'dopamine and estrogen receptor', 'high aerobic capacity and dopamine'.

RESULTS

1. Menopause and sarcopenia

Sarcopenia is defined as the age-related reduction in skeletal muscle mass and function and is considered one of the main contributors to morbidity and physical disability [9]. Menopause impacts sarcopenia, which not only affects very old women but also middle-aged women [10]. A sharp decrease in muscle mass and function occurs following the age of 50, about the years of menopausal transition [11]. The skeletal muscle is an important organ for energy expenditure and makes up about 50% of the human body. A gradual loss of skeletal muscle mass including reduced energy expenditure with mitochondrial dysfunction following menopause relates to an increase in visceral adipose tissue [12]. Therefore, sustaining skeletal muscle mass seems to be imperative to protect from menopause-associated metabolic syndrome in women.

Cross-sectional studies [13-15] including the research by the Study of Women's Health Across the Nation (SWAN) [13] reported that lean mass was lower in postmenopausal compared to premenopausal women. However, little was known about whether skeletal muscle mass and the prevalence of sarcopenia differ between the menopausal stages. Using a self-reported menstrual cycle assessment according to the Stages of Reproductive Aging Workshop (STRAW) criteria, our recent cross-sectional study [16] determined that peri-menopausal stage appears to be a vulnerable period for the significant loss of skeletal muscle mass. Our research team recruited 144 healthy women (aged 30-70 years) classified as 5 different menopausal stages: premenopausal, early/late perimenopausal, and early/late postmenopausal. Appendicular lean mass, measured using dual-energy x-ray absorptiometry, was 10 and 9 % lower in late peri- and post-menopausal, respectively, compared to early perimenopausal women. The prevalence of sarcopenia was 3 and 30% in early and late peri-menopausal women, respectively. Our findings showed a significant reduction in muscle mass and a rapid increase in the prevalence of sarcopenia from early to late peri-menopausal women, implying that muscle loss has already been started during peri-menopausal stage (i.e., menopausal transition). Our results highlight the necessity to investigate the major hormonal factors contributing to the loss of skeletal muscle mass and its further mechanisms.

2. Menopause, sex hormones, and physical inactivity

Menopause transition has been believed to trigger the underlying mechanisms associated with sarcopenia. This suggests that menopause transition may be a critical time to introduce strategies to lessen the significant loss of muscle mass and function, which can result in greater physical frailty and disability later in life. More studies are needed to elucidate the extent to which menopause augments sarcopenia, and if this muscular deterioration is associated with which sex hormones including estrogens. However, menopause is 1) the period that both estradiol and testosterone decrease; and 2) the consequence of both gonadal and chronologic aging. The complex, mixed changes in hormones and the aging process make it difficult to isolate a single cause of sarcopenia in older women. Accumulating evidence has suggested that alterations in the gonadal hormones during the menopause transition appear to be a strong determinant of skeletal muscle mass and strength in women. Among sex hormones, estrogen deficiency has been believed to be the most important clinical feature contributing to the development of sarcopenia [3]. Furthermore, assessment of estrogens and follicular stimulating hormone can confirm the diagnosis of menopause. The circulating levels of these hormones vary significantly during the menopause transition, such that the sharp reduction in estrogens and increase in follicular stimulating hormone occurs after the age of 50 in women [17].

Whereas the underlying mechanism of menopause-related changes in body composition are unclear, previous research suggests that reduced level of physical activity [18], rather than changes in food consumption

[19], likely plays a critical role in developing menopause-related loss of muscle mass and a consequent metabolic dysfunction. Women are more physically inactive than men, and research revealed that about 60% of women fail to meet the guidelines of physical activity [20]. This phenomenon of physical inactivity appears to be more profound in the aged compared to young women. In line with this trend, the number of women 65 years of age and older exhibits a greater prevalence of physical inactivity compared to aged men. Maintaining physically active is very important in aged women as an inverse association between mortality and physical activity has been reported [20]. Decreased physical activity level is known to impair aerobic fitness [21], which loss is a high risk factor for mortality [22].

Menopause impacts physical activity level in women, directly through the deterioration of skeletal muscle function and indirectly through behavioral changes such as reduced physical activity. Due to the incredible plasticity, skeletal muscle can be atrophied and eventually appears to be weak and malfunctioned following the less use of skeletal muscle. Preclinical rodent studies [23-27] using ovariectomy (OVX), a good model to study human menopause, support the menopausal phenomenon of physical inactivity in women. Ovariectomy resulted in a dramatic reduction in physical activity of 30-80% and this was not attributable to the effect of surgery. Physical activity was rescued in OVX rodents treated by estradiol add-back. The estrogenic regulation of physical activity was further supported by the observation that only estradiol but not progesterone add-back rescued physical activity to the normal level in OVX rodents [28]. These previous findings advocate the existence of a primary physiological factor resulting from menopause. Increasing evidence suggest that estradiol might be a major controller for behavioral modifications in women.

3. Dopamine signaling and physical activity

The dopamine (DA) signaling in the nucleus accumbens (NAc) is a key controller for voluntary activity [29-31]. Previous studies have implicated that mesolimbic dopamine circuits can significantly contribute to physical activity through the regulation of motivation [32], reward [33], and motor control [34]. Among the dopamine circuits, NAc is a part of the ventral striatum, a primary element in the affective processing of voluntary motor action [30]. In the striatum, DA neurons are responsible for the control of motor activity [31]. Also, DA signals in the NAc play a critical role in the behaviors related to natural reinforcers, e.g. food intake, incentive learning, and sexual behavior [35-37]. Physical activity was a natural and strong reinforcer prior to urbanization, primarily for food gathering and sexual behavior in women. Knab and Lightfoot [29] suggest that DA signal in the NAc is a key controller for voluntary running. Research on DA signal and the motivation of physical activity can be comparable to addiction studies [38,39]. The DA signal can deliver the rewarding and pleasurable feelings that can motivate to perform additional physical activity. This hypothesis is partially congruent with the previous studies using rodents. The rodent study using gene knock-out model found that DA transporter helps DA re-uptake into pre-synaptic site, while DA transporter gene deletion results in decreased voluntary activity [40]. Furthermore, DA knock-out rodents reduced motivation for high effortful tasks [41]. The study using specific agonist/antagonists demonstrated the importance of DA signal in regulating physical activity. They found that injecting the agonist for DA D1 receptor into the NAc enhances physical activity [42], whereas the antagonist injection reduced physical activity [43]. To sum up, it is suggested that DA signal and its activity regulate physical activity levels by changing motivation.

Two types of DA receptors, stimulatory and inhibitory, exist in dopamine neurons. The first is the DA D1-like stimulatory receptors (D1 and 5) containing no introns and acting by Gs-proteins to activate adenylyl cyclase, which increases cyclic adenosine monophosphate (cAMP) production and stimulates downstream neurons. The second is the DA D2-like inhibitory receptors (D 2, 3, and 4) containing introns and acting through Gi-proteins. These can inhibit adenylyl cyclase and in turn decrease cAMP production along with neural excitation [44,45]. While post-synaptic sites of the DA neuron possess both DA stimulatory and inhibitory receptors, the D2 and D3 auto-receptors are positioned at DA pre-synaptic site to inhibit DA activity and production [46]. Nearly most neurons of the brain showed DA receptor expression, however, the greater expression of the receptors has been found in nigrostriatal/mesolimbic circuits [47]. Interestingly, the estrogenic signal can regulate DA function in several steps for DA metabolism and its overall production at pre- and post- synaptic sites [48]. In the next session, using previous research, the author described the estrogen receptor (ER) regulation on DA signals and behaviors including voluntary physical activity.

4. Estrogen, estrogen receptors, and dopamine signaling

During menopausal transition, women experience menopausal symptoms including hot flashes, night sweats, and psychological changes but also the metabolic syndromes with weight gain and muscle loss, which are strongly associated with reduced estrogen level [6]. Among those

symptoms, psychological changes are critical as it can impact weight gain and muscle loss partially by reducing motivation to exercise in the consequence of physical inactivity. Menopause-associated reduction in physical activity has been considered as the brain-mediated pathway of estrogen deficiency. Estrogen may directly impact skeletal muscle or other cells via ER signaling [49] and also indirectly through behavioral changes (i.e., reduced physical activity including free-living activity and exercise-associated activity) [28,50]. Deficiency of estrogen attenuates voluntary running motivation along with impaired DA signals [28,51]. The regulation of voluntary running activity is attributed to levels of estrogen and its intact receptors in female rodents [52,53]. In rodents, OVX decreased levels of circulating estrogen and voluntary running distance to less than 1 km/day which is 5-10 times lower than pre-OVX rodents [28,51,53]. Estrogenic signal is the important mediator of physical activity in female, and Morgan et al. [54] suggests the possible role of estrogenic modulation for neurotransmitters including DA. Estrogen may provide a tonic stimulus for striatal DA receptors, while chronic stimulations maintains the activity of DA. The loss of this chronic stimulations following OVX was rescued by estrogen-based hormone replacement therapy, which conserved the upregulated stimulatory DA receptors when treated immediately after OVX [55,56]. In genomic regulation, a translocated ER directly binds to targeted DNA binding sites associated with enhancing DA receptor expression or other DA-related proteins [57].

DA is produced and secreted into the synaptic cleft using vesicles. DA activates either stimulatory D1-like (D1 & 5) or inhibitory D2-like (D2, 3, & 4) receptors. DA remained in the synaptic cleft is turned back to pre-synaptic terminal through DA transporter (DAT), and transformed to 3,4-dihydroxy-phenyl-acetic acid (DOPAC) via monoamine oxidase (MAO). Some of D2-like receptors are located at pre-synaptic terminal, and inhibits DA release. Most importantly, activated ERα generates and activates D1-like receptors, while it decreases D2-like receptors.

Estrogen mainly works through its receptors and most of all organs including skeletal muscle express ERs with ERα and β [58-60]. Pre-clinical studies using ER knock out rodents suggest ERα, but not ERβ, leads to impairments in metabolic health (i.e., glucose and insulin metabolism) [61,62], suggesting the important role of ERα. ERα also expresses in the brain, and is an obligatory link for OVX-induced reductions in voluntary physical activity [52]. At both pre- and post- synaptic regions, estrogen works in genomic pathway, a slow pathway via the translocation of ERα and β to nucleus [57]. In OVXed mice, decreased wheel running activity was rescued by estrogen-based hormone replacement therapy, whereas the treatment with phytoestrogen coumesterol having a similar affinity to estrogen through ERβ failed to alter wheel running behavior [63]. This finding suggests that, compared to ERα-, ERβ-pathway appears less involved in increased wheel running activity in OVX mice. Ogawa et al. [52] also demonstrated that estrogen-based hormone replacement therapy increased spontaneous cage activity in ERβ-, but not in ERα-KO mice. This also partially supports the hypothesis that estrogen-associated increase in spontaneous physical activity is mediated by ERα pathway. In line with the previous study, the implantation of estrogen into anterior hypothalamus including primarily ERα increases wheel running physical activity in OVX rats [64]. To our knowledge, however, none of the studies investigated the role of ERα pathway on DA receptor and activity, and whether the ERα–associated enhancement of DA activity results in enhanced voluntary running physical activity.

Despite the aforementioned phenomenon that menopause or OVX decreased ER signaling and activity, the early phase of post-menopause or OVX is accompanied by an instant, compensated up-regulation of ERs and aromatase, an enzyme responsible for the biosynthesis of estrogens, in the human mid-brain [65]. Such enhancement via *de novo* production of estrogens from cholesterol or testosterone is a key to compensate for the deficiency of circulating estrogens via the up-regulated ERα in a auto/paracrine way [65-67]. This compensatory mechanism of ERα and aromatase expressions were documented in OVX monkey [68] and rat brain cultures [69]. The compensatory mechanism of estrogen loss may play a critical role in the brain control prior to the body's adaptation to menopause. The lack of proper compensation may contribute to a significant health problem of the brain such as depression and dementia [65]. A study [70] using OVXed mice showed that the administration of aromatizable androgens attenuated the OVX-associated reduction in voluntary wheel running activity. Future studies are necessary to investigate the time window (i.e., early/late peri- or post-menopause) to which menopause or OVX impairs ERs and DA-related mRNA expressions and protein contents in the brain. By elucidating the time-dependent changes in molecular signals following menopause, future research can generate the optimal strategies to combat the menopause-associated health problems by more specific exercise prescription or hormone replacement therapy.

5. High running motivation and dopamine signaling

Women with high motivation to run may protect from the menopause-associated reduction in running capacity partially owing to greater

intrinsic motivation to run compared to sedentary or obese women. A previous study [71] partially supports our hypothesis in that high voluntary running rats, compared to low voluntary running rats, were physically active partially due to enhanced DA-associated transcriptomes in the NAc. In line with this study, compared to control mice, highly active mice showed greater DA activity in the mesolimbic DA circuit [72, 73]. Whereas the role of the NAc DA signaling in facilitating the rewarding nature of running has been somewhat reported, whether enhancing DA activity protects against the menopause or OVX-induced decrease in voluntary running is still vague. To test this, our group used the rats selectively bred for high aerobic capacity (HCR) and low aerobic capacity (LCR), which model was developed by researchers in the University of Michigan [74]. They found a unique divergence in running behavior between two rat lines, with a significant 5-fold greater voluntary running distance in HCR rats compared to LCR rats. Using this rat model, our group determined the potential role of NAc DA signaling in voluntary wheel running in OVXed female rats [75]. This study demonstrated that HCR rats had greater wheel running distance and the activation of dopamine signaling compared to LCR rats. While HCR rats gradually decreased their weekly running distance following OVX, LCR rats started low but gradually increased weekly running over 11 weeks. To investigate the underlying mechanism, we investigated their mRNA expressions in the NAc. We found that HCR rats had greater D1 stimulatory receptors and lower D3 and 4 inhibitory receptor mRNA expressions compared to LCR rats. However, OVX significantly up-regulated inhibitory dopamine receptors (i.e., D2 and 4 receptor mRNA expressions) in HCR rats, implying a strong effect of OVX independent of one's aerobic capacity or running motivation. More studies are needed to confirm our findings in clinical and other non-clinical research.

CONCLUSION

In women, menopause, the loss of estrogens, negatively impacts their physiology including behavioral changes such as depression along with physical inactivity. In this review, the author has described the underlying mechanism (s) by which changes in estrogen, estrogen receptors, and dopamine signaling contribute to physical activity level. The findings from our research and other previous studies demonstrated that estrogen receptor, specifically ERα, and dopamine receptors are the main controllers for voluntary physical activity. Furthermore, high running motivation is associated with enhanced dopamine activity, and more studies are needed to verify whether enhanced dopamine activity can protect against menopause-associated reduction in physical activity. Future studies should further investigate the specific mechanisms by which estradiol and estrogen receptors (ERα and β, and GPER) regulate brain signaling such as other neurotransmitters in mesolimbic circuits involved in exercise motivation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Y Park; Writing - original draft: N Kang, D Kim; Writing - review & editing: N Kang, D Kim.

ORCID

Nyeonju Kang	https://orcid.org/0000-0001-5185-9139
Dong-Il Kim	https://orcid.org/0000-0003-4434-799X
Young-Min Park	https://orcid.org/0000-0002-8297-7995

REFERENCES

1. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care. 2005;28(2):385-90.
2. Soares CN, Taylor V. Effects and management of the menopausal transition in women with depression and bipolar disorder. J Clin Psychiatry. 2007;68 Suppl 9:16-21.
3. Gohlke-Barwolf C. Coronary artery disease--is menopause a risk factor? Basic Res Cardiol. 2000;95 Suppl 1:I77-83.
4. Heidari R, Sadeghi M, Talaei M, Rabiei K, Mohammadifard N, et al. Metabolic syndrome in menopausal transition: Isfahan Healthy Heart Program, a population based study. Diabetol Metab Syndr. 2010;2:59.
5. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care. 2007;30(3):701-6.
6. Tandon VR, Mahajan A, Sharma S, Sharma A. Prevalence of cardio-

vascular risk factors in postmenopausal women: A rural study. J Midlife Health. 2010;1(1):26-9.
7. Despres JP. Abdominal obesity as important component of insulin-resistance syndrome. Nutrition. 1993;9(5):452-9.
8. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112(17):2735-52.
9. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50(5):889-96.
10. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12(4):249-56.
11. Aloia JF, McGowan DM, Vaswani AN, Ross P, Cohn SH. Relationship of menopause to skeletal and muscle mass. Am J Clin Nutr. 1991;53(6): 1378-83.
12. Wu SE, Chen WL. Transitional states of sarcopenia: the trajectory of fat accumulation and glucose fluctuation on risk of metabolic syndrome. Ann N Y Acad Sci 2021. doi:10.1111/nyas.14607.
13. Sternfeld B, Bhat AK, Wang H, Sharp T, Quesenberry CP, Jr. Menopause, physical activity, and body composition/fat distribution in midlife women. Med Sci Sports Exerc. 2005;37(7):1195-202.
14. Douchi T, Yamamoto S, Nakamura S, Ijuin T, Oki T, et al. The effect of menopause on regional and total body lean mass. Maturitas. 1998;29(3): 247-52.
15. Svendsen OL, Hassager C, Christiansen C. Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. Metabolism. 1995;44(3):369-73.
16. Park YM, Jankowski CM, Ozemek C, Hildreth KL, Kohrt WM, et al. Appendicular lean mass is lower in late compared with early perimenopausal women: potential role of FSH. J Appl Physiol. (1985). 2020;128(5):1373-80.
17. Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. Recent Prog Horm Res. 2002;57: 257-75.
18. Hardie DG. AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. Genes Dev. 2011;25(18):1895-908.
19. Nigro M, Santos AT, Barthem CS, Louzada RA, Fortunato RS, et al. A change in liver metabolism but not in brown adipose tissue thermogenesis is an early event in ovariectomy-induced obesity in rats. Endocrinology. 2014;155(8):2881-91.
20. Oguma Y, Sesso HD, Paffenbarger RS Jr., Lee IM. Physical activity and all cause mortality in women: a review of the evidence. Br J Sports Med. 2002;36(3):162-72.
21. Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. J Appl Physiol. 1985;111(5):1497-504.
22. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024-35.
23. Witte MM, Resuehr D, Chandler AR, Mehle AK, Overton JM. Female mice and rats exhibit species-specific metabolic and behavioral responses to ovariectomy. Gen Comp Endocrinol. 2010;166(3):520-8.
24. Rogers NH, Perfield JW, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and increased inflammation are early events in the development of ovariectomy-induced obesity. Endocrinology. 2009; 150(5):2161-8.
25. Mitsushima D, Takase K, Funabashi T, Kimura F. Gonadal steroids maintain 24 h acetylcholine release in the hippocampus: organizational and activational effects in behaving rats. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009;29(12): 3808-15.
26. Belsito KR, Vester BM, Keel T, Graves TK, Swanson KS. Impact of ovariohysterectomy and food intake on body composition, physical activity, and adipose gene expression in cats. J Anim Sci. 2009;87(2): 594-602.
27. Hertrampf T, Seibel J, Laudenbach U, Fritzemeier KH, Diel P. Analysis of the effects of oestrogen receptor alpha (ERalpha)- and ERbeta-selective ligands given in combination to ovariectomized rats. Br J Pharmacol. 2008;153(7):1432-7.
28. Gorzek JF, Hendrickson KC, Forstner JP, Rixen JL, Moran AL, et al. Estradiol and tamoxifen reverse ovariectomy-induced physical inactivity in mice. Med Sci Sports Exerc. 2007;39(2):248-56.
29. Knab AM, Lightfoot JT. Does the difference between physically active and couch potato lie in the dopamine system? Int J Biol Sci. 2010;6(2): 133-50.
30. Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. Prog

Neurobiol. 1980;14(2-3):69-97.

31. Salamone JD, Keller RW, Zigmond MJ, Stricker EM. Behavioral activation in rats increases striatal dopamine metabolism measured by dialysis perfusion. Brain Res. 1989;487(2):215-24.
32. Owesson-White CA, Cheer JF, Beyene M, Carelli RM, Wightman RM. Dynamic changes in accumbens dopamine correlate with learning during intracranial self-stimulation. Proc Natl Acad Sci U S A. 2008;105(33):11957-62.
33. Schultz W. Updating dopamine reward signals. Curr Opin Neurobiol. 2013;23(2):229-38.
34. Salamone JD. Complex motor and sensorimotor functions of striatal and accumbens dopamine: involvement in instrumental behavior processes. Psychopharmacology (Berl). 1992;107(2-3):160-74.
35. Salamone JD, Cousins MS, Snyder BJ. Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. Neurosci Biobehav Rev. 1997;21(3):341-59.
36. Lett BT, Grant VL, Byrne MJ, Koh MT. Pairings of a distinctive chamber with the aftereffect of wheel running produce conditioned place preference. Appetite. 2000;34(1):87-94.
37. Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol. 1996;6(2):228-36.
38. Pierce RC, Kumaresan V. The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? Neurosci Biobehav Rev. 2006;30(2):215-38.
39. George SR, Fan T, Ng GY, Jung SY, O'Dowd BF, et al. Low endogenous dopamine function in brain predisposes to high alcohol preference and consumption: reversal by increasing synaptic dopamine. J Pharmacol Exp Ther. 1995;273(1):373-9.
40. Spielewoy C, Biala G, Roubert C, Hamon M, Betancur C, et al. Hypolocomotor effects of acute and daily d-amphetamine in mice lacking the dopamine transporter. Psychopharmacology (Berl). 2001;159(1):2-9.
41. Cousins MS, Atherton A, Turner L, Salamone JD. Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. Behav Brain Res. 1996;74(1-2):189-97.
42. De Vries TJ, Cools AR, Shippenberg TS. Infusion of a D-1 receptor agonist into the nucleus accumbens enhances cocaine-induced behavioural sensitization. Neuroreport. 1998;9(8):1763-8.
43. Baldo BA, Sadeghian K, Basso AM, Kelley AE. Effects of selective dopamine D1 or D2 receptor blockade within nucleus accumbens subregions on ingestive behavior and associated motor activity. Behav Brain Res. 2002;137(1-2):165-77.
44. Lee D, Huang W, Lim AT. Dopamine induces a biphasic modulation of hypothalamic ANF neurons: a ligand concentration-dependent effect involving D5 and D2 receptor interaction. Mol Psychiatry. 2000;5(1):39-48.
45. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. Physiol Rev. 1998;78(1):189-225.
46. Madularu D, Shams WM, Brake WG. Estrogen potentiates the behavioral and nucleus accumbens dopamine response to continuous haloperidol treatment in female rats. Eur J Neurosci. 2014;39(2):257-65.
47. Dearry A, Gingrich JA, Falardeau P, Fremeau RT, Jr., Bates MD, et al. Molecular cloning and expression of the gene for a human D1 dopamine receptor. Nature. 1990;347(6288):72-6.
48. Di Paolo T. Modulation of brain dopamine transmission by sex steroids. Rev Neurosci. 1994;5(1):27-41.
49. Wend K, Wend P, Krum SA. Tissue-Specific Effects of Loss of Estrogen during Menopause and Aging. Front Endocrinol (Lausanne). 2012;3:19.
50. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond). 2008;32(6):949-58.
51. Kadi F, Karlsson C, Larsson B, Eriksson J, Larval M, et al. The effects of physical activity and estrogen treatment on rat fast and slow skeletal muscles following ovariectomy. J Muscle Res Cell Motil. 2002;23(4):335-9.
52. Ogawa S, Chan J, Gustafsson JA, Korach KS, Pfaff DW. Estrogen increases locomotor activity in mice through estrogen receptor alpha: specificity for the type of activity. Endocrinology. 2003;144(1):230-9.
53. Morgan MA, Pfaff DW. Effects of estrogen on activity and fear-related behaviors in mice. Horm Behav. 2001;40(4):472-82.
54. Morgan MA, Schulkin J, Pfaff DW. Estrogens and non-reproductive behaviors related to activity and fear. Neurosci Biobehav Rev. 2004;28(1):55-63.
55. Levesque D, Di Paolo T. Chronic estradiol treatment increases ovariectomized rat striatal D-1 dopamine receptors. Life Sci. 1989;45(19):1813-20.
56. Kharchilava OM, Valeeva LA. Effects of surgical ovariectomy on dopamine receptors of the heart and brain. Patol Fiziol Eksp Ter. 2008;(4):21-3.
57. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev. 2013;34(3):309-38.

58. Lemoine S, Granier P, Tiffoche C, Rannou-Bekono F, Thieulant ML, et al. Estrogen receptor alpha mRNA in human skeletal muscles. Med Sci Sports Exerc. 2003;35(3):439-43.
59. Wiik A, Ekman M, Johansson O, Jansson E, Esbjornsson M. Expression of both oestrogen receptor alpha and beta in human skeletal muscle tissue. Histochem Cell Biol. 2009;131(2):181-9.
60. Barros RP, Gustafsson JA. Estrogen receptors and the metabolic network. Cell Metab. 2011;14(3):289-99.
61. Bryzgalova G, Gao H, Ahren B, Zierath JR, Galuska D, et al. Evidence that oestrogen receptor-a plays an important role in the regulation of glucose homeostasis in mice: insulin sensitivity in the liver. Diabetologia. 2006;49:588-97.
62. Ribas V, Nguyen MT, Henstridge DC, Nguyen AK, Beaven SW, et al. Impaired oxidative metabolism and inflammation are associated with insulin resistance in ERalpha-deficient mice. Am J Physiol Endocrinol Metab. 2010;298(2):E304-19.
63. Garey J, Morgan MA, Frohlich J, McEwen BS, Pfaff DW. Effects of the phytoestrogen coumestrol on locomotor and fear-related behaviors in female mice. Horm Behav. 2001;40(1):65-76.
64. Fahrbach SE, Meisel RL, Pfaff DW. Preoptic implants of estradiol increase wheel running but not the open field activity of female rats. Physiol Behav. 1985;35(6):985-92.
65. Ishunina TA, Fischer DF, Swaab DF. Estrogen receptor alpha and its splice variants in the hippocampus in aging and Alzheimer's disease. Neurobiol Aging. 2007;28(11):1670-81.
66. Do Rego JL, Seong JY, Burel D, Leprince J, Luu-The V, et al. Neurosteroid biosynthesis: enzymatic pathways and neuroendocrine regulation by neurotransmitters and neuropeptides. Front Neuroendocrinol. 2009;30(3):259-301.
67. Simpson ER, Misso M, Hewitt KN, Hill RA, Boon WC, et al. Estrogen--the good, the bad, and the unexpected. Endocr Rev. 2005;26(3):322-30.
68. Higaki S, Takumi K, Itoh M, Watanabe G, Taya K, et al. Response of ERbeta and aromatase expression in the monkey hippocampal formation to ovariectomy and menopause. Neurosci Res. 2012;72(2):148-54.
69. Prange-Kiel J, Wehrenberg U, Jarry H, Rune GM. Para/autocrine regulation of estrogen receptors in hippocampal neurons. Hippocampus. 2003;13(2):226-34.
70. Roy EJ, Wade GN. Role of estrogens in androgen-induced spontaneous activity in male rats. J Comp Physiol Psychol. 1975;89(6):573-9.
71. Roberts MD, Brown JD, Company JM, Oberle LP, Heese AJ, et al. Phenotypic and molecular differences between rats selectively bred to voluntarily run high vs. low nightly distances. Am J Physiol Regul Integr Comp Physiol. 2013;304(11):R1024-35.
72. Fink JS, Reis DJ. Genetic variations in midbrain dopamine cell number: parallel with differences in responses to dopaminergic agonists and in naturalistic behaviors mediated by central dopaminergic systems. Brain Res. 1981;222(2):335-49.
73. Waters RP, Renner KJ, Pringle RB, Summers CH, Britton SL, et al. Selection for aerobic capacity affects corticosterone, monoamines and wheel-running activity. Physiol Behav. 2008;93(4-5):1044-54.
74. Monroe DC, Holmes PV, Koch LG, Britton SL, Dishman RK. Striatal enkephalinergic differences in rats selectively bred for intrinsic running capacity. Brain Res. 2014;1572:11-7.
75. Park YM, Kanaley JA, Padilla J, Zidon T, Welly RJ, et al. Effects of intrinsic aerobic capacity and ovariectomy on voluntary wheel running and nucleus accumbens dopamine receptor gene expression. Physiol Behav. 2016;164(Pt A):383-9.