Ogawa , Toxicol :Open Access 2021, 7:2

Toxicology : Open Access

Case Report Open Access

A Review on the Sex Difference in Lipotoxicity in Peripheral Nerves

Masahiro Ogawa*

Life Science Research Institute, Kumiai Chemical Industry, Shizuoka, Japan

***Corresponding author:** Masahiro Ogawa, Life Science Research Institute, Kumiai Chemical Industry, Shizuoka, Japan, Tel: +81537353160; E-mail: m-ogawa@kumiai-chem.co.jp

Received date: March 05, 2021; **Accepted date:** March 12, 2021; **Published date:** March 26, 2021

Abstract

Obesity is caused as the consequence of positive energy balance, which increases the amount of lipid in adipose tissue. The intake of excessive amounts of fatty acids is considered to be a risk factor for cardiovascular diseases, insulin resistance, dyslipidemia, and obesity. Males and females experience many diseases and disorders differently. Sex hormones, such as estrogen, progesterone, and androgen, contribute to the sex differences in body weight and metabolism between males and females and are thought to be responsible for sex-specific differences. Several studies have shown that the sex-specific adverse effects were observed in peripheral nerves. This review focuses on the sex difference in lipotoxicity in peripheral nerves. High-fat diet feeding promotes oxidative stress and inflammation in animal models. In male mice fed the high-fat diet, the pathogenesis of neuropathy is enhanced in the sciatic nerves. The high-fat diet induced apoptosis in the sciatic nerves of male, but not female. In ovariectomized female mice, a high-fat diet induces the apoptosis marker. On the other hand, estrogen attenuates high-fat diet-induced apoptosis markers in the sciatic nerve of ovariectomized female mice. Therefore, there indicate that estrogen is a key factor for the sex difference in peripheral nervous disorder. In vitro studies have reported that estrogen-activated ERα prevents the fatty acid-induced oxidative stress and inflammation and has the inhibitory effects of fatty acid-enhanced apoptosis and autophagy in peripheral nerves. On the other hand, a recent study has reported that ERβ promotes autophagy in neural cells. These suggest that ERβ may have the opposite effects of ERα in neural cells. Further studies are needed to understand the role of ER isoforms in neuron injury.

Keywords: Sex difference; High-fat diet; Lipotoxicity; Estrogen; Cell death; Peripheral nerves

Introduction

Obesity is caused as the consequence of positive energy balance, which increases the amount of lipid in adipose tissue. The intake of excessive amounts of fatty acids promote lipotoxicity, consequently increases the risk for cardiovascular diseases, insulin resistance, dyslipidemia, diabetes, and obesity. The percentage of patients with peripheral neuropathy was more frequent in groups with the high Body Mass Index (BMI) (≥ 30 kg/m^2) compared to the low BMI (<30 kg/m^2) [1]. Free fatty acids accelerate mitochondrial fission and promote Reactive Oxygen Species (ROS) production [2]. ROS-induced oxidative stress promotes dysfunction in peripheral nerves [3]. Thus, it is assumed that lipotoxicity enhances the development of peripheral neuropathy.

Obviously, males and females experience many diseases and disorders differently. Sex hormones, such as estrogen, progesterone, and androgen, contribute to the sex differences in metabolism between males and females and are thought to be responsible for sex-specific differences [4,5]. Several studies have reported that the sex-specific adverse effects were observed in peripheral nerves [6-10].This review focuses on the sex difference in lipotoxicity in peripheral nerves.

The Involvement of Signaling of Cell Death in Peripheral Neuropathy by Fatty Acids

Peripheral neuropathy, a result of damage to peripheral nerves, frequently causes numbness and pain, in the whole body, particularly extremities. The major categories of peripheral nerve injury (neuropathy) are generally neuronopathy, axonopathy, and myelinopathy [11]. Neuronopathy is induced by cell death such as apoptosis and/or autophagy in the cell body of neurons [12,13]. In axonopathy, axon degeneration will lead to secondary loss of the myelin sheath. Myelinopathy is caused by the destruction of the myelin sheath. Apoptosis is a programmed mechanism of cell death that is triggered in response to cellular stress. BCL2 family proteins, such as BAX and BCL2, are key regulators of apoptosis. BAX-activated Caspase-3 initiates DNA fragmentation, thereby leading to cell death. On the other hand, autophagy is a lysosomal degradation pathway. Autophagy can be either non-selective or selective. In selective autophagy, autophagy receptors bind to cargoes and result in degradation within lysosomes/vacuoles, depending on the core autophagy machinery. p62/SQSTM1 is a key autophagy receptor that can shuttle ubiquitinated cargo for autophagic degradation.

Fatty acids are chemically classified as saturated and unsaturated, and each of them has specific biological functions. Interestingly, saturated fatty acids induce apoptosis [14] and unsaturated fatty acids induce autophagy [15]. Recently, Ogawa et al. also reported that saturated fatty acid-induced apoptosis marker and unsaturated fatty acid increased the level of the autophagy-related gene in neural cells [16,17]. However, the mechanism by which fatty acids induce different molecular cell death (apoptosis and autophagy) dependent on saturation remains unclear. In animal studies, High-Fat Diets (HFD) rich in both saturated and unsaturated fatty acids are often used to induce obesity, and many studies have reported that the HFD induces apoptosis in hepatocytes and cardiomyoblasts [18]. Similarly, Ogawa et al. recently reported that the HFD induced the increase of apoptosis markers in the peripheral nerves.In neural cells, the treatment of fatty

acids induced protein expression of BAX and the number of apoptotic cells [19]. By contrast, mice fed the HFD have reduced hepatic autophagy [20]. The HFD inhibits autophagy in cardiomyocytes. Therefore, the mixtures of saturated and unsaturated fatty acids probably induce apoptosis but not autophagy

Sex Difference in Lipotoxicity in Peripheral Nerves

Sex hormones, such as estrogen, progesterone, and androgen, contribute to the sex differences in metabolism between males and females and are responsible for sex-specific differences. The pathogenesis of neuropathy is enhanced in the sciatic nerves of male mice fed the HFD. Male mice are more vulnerable than the females to the impacts of the HFD on weight gain, metabolic alterations and deficits of learning, and hippocampal synaptic plasticity. Male rats with diabetes have a higher frequency of neuropathy than female rats with diabetes [21]. Similarly, male mice develop a greater extent of diabetes-induced cognition deficits and peripheral neurovascular dysfunction than female mice [22]. In our recent study, HFD induced apoptosis in the sciatic nerves of males, but not females. Therefore, these indicate that there is a sex difference in peripheral neuropathy.

In ovariectomized females fed the HFD, the levels of the apoptosis-related genes were increased compared to ovariectomized mice fed a normal diet. In contrast, the replacement of estrogen, a female hormone, in ovariectomized mice abolished the HFD-induced mRNA levels of two apoptosis-related genes.Thus, it is assumed that estrogen has prevented the cell damage of central and peripheral nerves.

The Role of Estrogen Receptor Isoform in the Peripheral Nerve Injury by Lipotoxicity

Estrogen signaling is mediated by binding to estrogen receptor α (ERα) and/or ERβ, which are a member of the nuclear receptor family. The function of estrogen can be mediated by direct binding of estrogen receptor complexes to specific sequences in gene promoters (genomic effects), or by mechanisms that do not involve direct binding to DNA (non-genomic effects). Estrogen prevents apoptosis *via* ERs-mediated non-genomic actions in many cell types [23]. Both ERα and ERβ are expressed in the brain [24] and peripheral neurons [25]. ERs are necessary for the embryonic development of the brain.

Fatty acids induce oxidative stress and inflammation, consequently lead to cell death [26,27]. Estrogen mediates neuroprotection and anti-inflammatory effects through ERα signaling on astrocytes and neurons [28]. Estrogen also attenuates ischemic oxidative damage *via* an ERα-mediated inhibition of NADPH oxidase activation [29]. In short, estrogen exerts anti-inflammatory and anti-oxidant properties. Cerebral ischemia is followed by a local inflammatory response that contributes to tissue damage. The harmful effects are caused due to excess *nitric oxide* (NO) production by the inducible isoform of NO synthase (iNOS). Another study has shown that the decrease of iNOS expression by estrogen is one of the factors mediating the resistance to cerebral ischemia in females [30]. In female rats, the HFD led to increased iNOS expression and decreased levels of estrogen and ERα protein in the HFD-fed group [31]. Estrogen and ERα-selective agonist, but not ERβ-selective agonist, prevented the oleic acid-induced cytotoxicity in Neuro-2a neural cells. Thus, these indicate that estrogen prevents the fatty acid-induced oxidative stress and inflammation via ERα in peripheral nerves.

Oleic acid, an unsaturated fatty acid, induced autophagy but had a minimal effect on apoptosis. In contrast, palmitic acid, a saturated fatty acid, was suppressed autophagy, and significantly induced apoptosis in hepatocytes. Neuroprotective effects of estrogen in the peripheral neuron are partly related to the suppression of excessive autophagy [32]. The knockdown of ERα induces autophagy and promotes ROS-induced cell death in breast cancer cells [33], therefore estrogen inhibits autophagy *via* ERα. Estrogen inhibited the oleic acid has induced cytotoxicity, and enhanced the stearic acid induced cytotoxicity at high concentrations. On the other hand, ERβ-selective agonist slightly enhanced the oleic acid-induced cytotoxicity and induced the increase of p62/Sqstm1 mRNA in Neuro-2a neural cells . ERα and ERβ are known to undertake different effects in various tissues [34,35]. A recent study has reported that ERβ promotes autophagy in neural cells [36]. Therefore, these suggest that estrogen plays probably the different roles between saturated fatty acids and unsaturated fatty acids, and ERβ may have the opposite effects of ERα in neural cells. Further studies are needed to understand the role of ER isoforms in neuron injury.

Conclusion

HFD-induced lipotoxicity enhances the development of peripheral neuropathy in males only. In females, estrogen attenuated HFD feeding damaged the sciatic nerves. In short, estrogen is assumed to be responsible for sex differences in the injury of sciatic nerves. In vitro studies indicate that estrogen plays probably the different roles between saturated fatty acids and unsaturated fatty acids. In neural cells, ERα prevents the saturated fatty acid-induced cytotoxicity by the inhibitory effects of oxidative stress and inflammation, and ERβ promotes cytotoxicity. ERα and ERβ are known to exert different effects in various tissues. Therefore, ERβ may have the opposite effects of ERα in neural cells. Further studies are needed to understand the role of ER isoforms in neuron injury.

References

1. Herrera-Rangel A, Aranda-Moreno C, Mantilla-Ochoa T, Zainos-Saucedo L, Jáuregui-Renaud K (2014) The influence of peripheral neuropathy, gender, and obesity on the postural stability of patients with type 2 diabetes mellitus. J Diabetes. 2014:787202
2. Inoguchi T, Li P, Umeda F, Yu HY, Kakimoto M (2000) High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells. Diabetes. 49:1939-1945.
3. Mallet ML, Hadjivassiliou M, Sarrigiannis PG, Zis P (2020) The role of oxidative stress in peripheral neuropathy. J Mol Neurosci. 70: 1009-1017.
4. Ogawa M, Kitakaze T, Harada N, Yamaji R (2015) Female-specific regulation of skeletal muscle mass by USP19 in young mice. J Endocrinol. 225: 135-145.
5. True C, Abbott DH, Roberts CT Jr, Varlamov O (2017) Sex differences in androgen regulation of metabolism in nonhuman primates. Adv Exp Med Biol. 1043: 559-574.
6. Rumora AE, LoGrasso G, Hayes JM, Mendelson FE, Tabbey MA, et al (2019) The divergent roles of dietary saturated and monounsaturated fatty acids on nerve function in murine models of obesity. J Neurosci. 39: 3770-3781.
7. Hwang LL, Wang CH, Li TL, Chang SD, Lin LC, Chen CP, et al (2010) Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. Obesity (Silver Spring). 18: 463-469.

8. Robison LS, Albert NM, Camargo LA, Anderson BM, Salinero et al (2020) High-fat diet-induced obesity causes sex-specific deficits in adult hippocampal neurogenesis in mice. ENEURO. 7: 0391-0319.
9. Morselli E, Frank AP, Palmer BF, Rodriguez-Navas C, Criollo A, et al (2016) A sexually dimorphic hypothalamic response to chronic high-fat diet consumption. Int J Obes (Lond). 40: 206-209.
10. Ogawa M, Kimura T, Tanetani Y, Hori M, Kyoya T, et al (2020) Sex differences in the effects of high-fat diet on mouse sciatic nerves. Fundam Toxicol Sci. 7: 133-139.
11. Peltier AC, Russell JW (2006) Advances in understanding drug-induced neuropathies. Drug Saf. 29: 23-30.
12. Nixon RA, Yang DS (2012) Autophagy and neuronal cell death in neurological disorders. Cold Spring Harb Perspect Biol. 4: a008839.
13. Ogawa M, Kimura T, Kitamoto J, Takeda T, Kitazumi K, Kyoya T, Terada M (2020) A screening system for detection of neurotoxic potency of chemicals using in vitro model. Toxicol Int. 27: 44-53
14. Mei S, Ni HM, Manley S, Bockus A, Kassel KM, et al (2011) Differential roles of unsaturated and saturated fatty acids on autophagy and apoptosis in hepatocytes. J Pharmacol Exp Ther. 339: 487-498.
15. Niso-Santano M, Malik SA, Pietrocola F, Bravo-San Pedro JM, Mariño G, et al (2015) Unsaturated fatty acids induce non-canonical autophagy. EMBO J. 34: 1025-1041.
16. Ogawa M, Kyoya T, Kimura T, Terada M (2020) Effects of estrogen on fatty-acid-induced cytotoxicity in mouse Neuro-2a neural cells. Fundam Toxicol Sci. 7: 115-121.
17. Wang Y, Ausman LM, Russell RM, Greenberg AS, Wang XD (2008) Increased apoptosis in high-fat diet-induced nonalcoholic steatohepatitis in rats is associated with c-Jun NH2-terminal kinase activation and elevated proapoptotic Bax. J Nutr. 138: 1866-1871.
18. Hsu HC, Chen CY, Lee BC, Chen MF (2016) High-fat diet induces cardiomyocyte apoptosis via the inhibition of autophagy. Eur J Nutr. 55: 2245-2254.
19. Yuan Q, Zhao S, Wang F, Zhang H, Chen ZJ, et al (2013) Palmitic acid increases apoptosis of neural stem cells via activating c-Jun N-terminal kinase. Stem Cell Res. 10: 257-266.
20. Liu HY, Han J, Cao SY, Hong T, Zhuo D, et al (2009) Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia: inhibition of FoxO1-dependent expression of key autophagy genes by insulin. J Biol Chem. 284: 31484-31492.
21. Stenberg L, Dahlin LB (2014) Gender differences in nerve regeneration after sciatic nerve injury and repair in healthy and in type 2 diabetic Goto-Kakizaki rats. BMC Neurosci. 15: 107.
22. Fan B, Liu XS, Szalad A, Wang L, Zhang R, et al (2018) Influence of sex on cognition and peripheral neurovascular function in diabetic mice. Front Neurosci. 12: 795.
23. Li D, Chen J, Ai Y, Gu X, Li L, et al (2019) Estrogen-related hormones induce apoptosis by stabilizing schlafen-12 protein turnover. Mol Cell. 75: 1103-1116.
24. Broughton BR, Brait VH, Guida E, Lee S, Arumugam TV, et al (2013) Stroke increases g protein-coupled estrogen receptor expression in the brain of male but not female mice. Neurosignals. 21: 229-239.
25. Gu Y, Wu Y, Su W, Xing L, Shen Y,et al (2018) 17β-Estradiol enhances schwann cell differentiation via the erβ-erk1/2 signaling pathway and promotes remyelination in injured sciatic nerves. Front Pharmacol. 9: 1026.
26. Ryter SW, Kim HP, Hoetzel A, Park JW, Nakahira K, et al (2007) Mechanisms of cell death in oxidative stress. Antioxid Redox Signal. 9: 49-89.
27. Yang Y, Jiang G, Zhang P, Fan J (2015) Programmed cell death and its role in inflammation. Mil Med Res. 2: 12.
28. Spence RD, Wisdom AJ, Cao Y, Hill HM, Mongerson CR, et al (2013) Estrogen mediates neuroprotection and anti-inflammatory effects during EAE through ERα signaling on astrocytes but not through ERβ signaling on astrocytes or neurons. J Neurosci. 33: 10924-10933.
29. Zhang QG, Raz L, Wang R, Han D, De Sevilla L, et al (2009) Estrogen attenuates ischemic oxidative damage via an estrogen receptor alpha-mediated inhibition of NADPH oxidase activation. J Neurosci. 29: 13823-13836.
30. Park EM, Cho S, Frys KA, Glickstein SB, Zhou P, et al (2006) Inducible nitric oxide synthase contributes to gender differences in ischemic brain injury. J Cereb Blood Flow Metab. 26: 392-401.
31. Jovanovic A, Sudar-Milovanovic E, Obradovic M, Pitt SJ, Stewart AJ, et al (2017) Influence of a high-fat diet on cardiac iNOS in female rats. Curr Vasc Pharmacol. 15: 491-500.
32. Lin CW, Chen B, Huang KL, Dai YS, Teng HL (2016) Inhibition of autophagy by estradiol promotes locomotor recovery after spinal cord injury in rats. neurosci bull. 32: 137-144.
33. Cook KL, Clarke PA, Parmar J, Hu R, Schwartz-Roberts JL, et al (2014) Knockdown of estrogen receptor-α induces autophagy and inhibits antiestrogen-mediated unfolded protein response activation, promoting ROS-induced breast cancer cell death. FASEB J. 28: 3891-3905.
34. Hayashi SI, Eguchi H, Tanimoto K, Yoshida T, Omoto Y, et al (2003) The expression and function of estrogen receptor alpha and beta in human breast cancer and its clinical application. Endocr Relat Cancer. 10: 193-202.
35. Ogawa M, Yamaji R, Higashimura Y, Harada N, Ashida H, et al (2011) 17β-estradiol represses myogenic differentiation by increasing ubiquitin-specific peptidase 19 through estrogen receptor α. J Biol Chem. 286: 41455-41465.
36. Wei Y, Zhou J, Wu J, Huang J (2019) ERβ promotes Aβ degradation via the modulation of autophagy. Cell Death Dis. 10: 565.