Ann Appl Physiol, 1: e28, 2024.
http://www.aapjournal.com; e-ISSN: 3060-6373; p-ISSN: 2476-7662. 10.61186/aapjournal.28

Review Article

Exercise Training and Obesity: The Role of Semaphorin 3E/Plexin D1 Axis: A Brief Review

[1]Arash Khodamoradi[♣], [2]Abedin Khosravi, [3]Patricia K. Doyle-Baker, [4,5]Abderraouf Ben Abderrahman, [6]Eugenia Murawska-Ciałowicz, [7]Anthony C. Hackney, [8]Kelly E. Johnson, [9]Ayoub Saeidi

[1]Department of Exercise Physiology, Faculty of Sports Sciences and Physical Education, University of Mazandaran, Babolsar, Iran. [2]Department of Physical Education and Sport Science, Payame Noor University, Iran. [3]Human Performance Lab, Faculty of Kinesiology, University of Calgary, Alberta, Canada. [4] Higher Institute of Sport and Physical Education of Ksar-Said, University of Manouba, Cité Nasr, Tunisia. [5]Tunisian Research Laboratory "Sports Performance Optimization", National Center of Medicine and Science in Sports (CNMSS), Tunis, Tunisia. [6]University School of Physical Education, Physiology and Biochemistry Department, Wrocław, Poland. [7]Department of Exercise & Sport Science, University of North Carolina, Chapel Hill, NC, USA. [8]Department Kinesiology, Coastal Carolina University, Conway, SC, USA. [9]Department of Physical Education and Sport Sciences, Faculty of Humanities and Social Sciences, University of Kurdistan, Sanandaj, Iran.

Submitted March 30, 2023; Accepted in final form May 22, 2023.

ABSTRACT

Background. Adipokines play a significant role in autocrine/paracrine regulation of adipocyte differentiation, metabolism, and local inflammatory responses. They also regulate the systemic metabolism of fat and glucose through the intracellular/systemic action of the brain, liver, and muscle. Semaphorin 3E (Sema3E) is a novel adipokine essential to obesity and related diseases. Sema3E is an exception among semaphorin proteins and depends on a specific Plexin D1 receptor (Plexin D1). **Objectives.** This brief review synthesizes the current knowledge dealing with the role that Sema3E and Plexin D1 can play in response to physical exercise effects in individuals with obesity. M**ethods.** A brief narrative review is used to reach the aim of the study. **Results.** Some scientific evidence may suggest a positive influence of physical exercise training on Semaphorin 3E/Plexin D1 Axis levels. **Conclusions.** However, physical exercise has a role in these factors that must be investigated to improve our understanding of the role of inflammation in obesity and insulin resistance.

KEYWORDS: ***Obesity, Adipokines, Semaphorins, Adipocyte Cytokines, Physical Activity.***

INTRODUCTION

Obesity, insulin resistance, and type 2 diabetes are contributing to pan-epidemic levels of metabolic diseases and becoming the leading causes of death worldwide (1, 2). Obesity is accompanied by visceral fat infiltration and impairment of aspects of metabolic regulation by select immune cells, specifically macrophages (3). Accumulating adipose tissue undergoes extensive rehabilitation and macrophage invasion, disrupting tissue homeostasis (4).

♣. Corresponding Author:
Arash Khodamorad, Ph.D.
E-mail: arash.khodamoradi@yahoo.com

Adipose tissue macrophages secrete inflammatory cytokines, in particular tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL-6), which influence chronic inflammation and contribute to the development of systemic insulin resistance (3). Hence, adipose tissue is viewed as an active endocrine organ, producing several signaling peptides with many biological functions with both positive and negative impacts on homeostasis (5-8).

The signaling molecules called adipokines (adipocyte cytokines) (9, 10) play a key role in autocrine/paracrine regulation of adipocyte differentiation, metabolism, and local inflammatory responses (11, 12). They also regulate the systemic metabolism of fat and glucose through the intracellular/systemic action of the brain, liver, and muscle. Adipokine levels in serum and secretion are significantly affected by the number and size of adipocytes (13, 14). Semaphorin 3E (Sema3E) is a novel adipokine essential in obesity and related diseases (15). Nishide et al. identified Sema3E as a potent regulator of adipose tissue macrophage accumulation, thereby contributing to systemic insulin resistance (16). Class 3 Semaphorins are secreted and membrane proteins that can mediate both excitatory and absorbing signals through various receptors in the plexin or neuropilin families (17). Sema3s do not directly interact with the plexin receptor but instead interact with neuropilin-1 (Nrp1) or Nrp2, resulting in the assembly and activation of the Nrp-plexinA (or Nrp-plexinD1) holoreceptor complex (18). Sema3E is an exception among semaphorin proteins and depends on a specific Plexin D1 receptor (Plexin D1) (19). The Sema3E expression is significantly concentrated in adipocytes, while the Plexin D1 receptor is observed in both adipocytes and accumulated macrophages (20). This brief review aims to synthesize the current knowledge dealing with the role that Sema3E and Plexin D1 can play in response to physical exercise effects in individuals with obesity.

NUTRIENT SENSING AND IMMUNE SIGNALING

Sema3E and Plexin D1 are essential in the inflammatory response of adipose tissue, particularly when a high-calorie diet is consumed, i.e., which are associated with various metabolic disorders (21). For example, the Sema 3E-Plexin D1 axis is up-regulated in adipose tissue of obese people (4). Schmidt and Moore used a diet-induced obesity model (DIO) to investigate the role of semaphorins and plexins in adipose tissue inflammation by feeding mice with a high fat/ high sucrose (HFHS) diet (4). Findings indicated that compared to mice with a regular diet, those on HFHS had an increase in the penetration of single-core cells into visceral fat. Schmidt et al. also investigated the protein expression of semaphorins in various tissues of DIO mice, showing that Sema3E expression was significantly increased, as was Plexin D1 in adipose tissue (4). All these results were accompanied by an increase in plasma Sema3E levels, indicating a potential interaction between secretion of Sema3E by adipose tissue and the expression of Plexin D1 by macrophages.

Sema3E plasma levels have also increased in patients with diabetes, indicating the potential role of the Sema3E-Plexin D1 axis in metabolic diseases. Schmidt and Moore found that Sema3E overexpression causes adipose tissue inflammation by generating adipocyte-specific Sema3E transgenic mice (4). They used a construct containing full-length Sema3e cDNA driven by the Fabp4 promoter and fed them a standard diet (4). These mice showed a significant increase in Sema3E expression in their adipose tissue, and plasma Sema3E levels were significantly higher than in the control group (4). Moreover, Sema3E inhibited insulin signaling in adipocytes by blocking Akt phosphorylation.

In another study, Shimizu et al. also observed a selective increase in the Sema3E expression in the visceral adipose tissue of high-fat-diet-fed mice, and this paralleled an increase in serum levels of Sema3E (20). Based on this, it seems that Sema3E secretion results in the spread of adipose tissue in adipocytic macrophages and the action of adipocytic pathogens that cause insulin resistance. In contrast, overexpression of Sema3E by a specific lipid inducer instead of adipose tissue macrophage accumulation resulted in insulin resistance and glucose intolerance in chow-fed mice (4).

The elimination of Sema3E improves diet-induced lipid inflammation and metabolic abnormalities. Similarly, patients with diabetes show increased plasma Sema3E, which may play a role in Sema3E-Plexin D1 signaling in human metabolic diseases (20). In mice, injections of

Plexin D1 were sufficient to reciprocate the effects of Sema3E in obesity, including accumulation of adipose tissue macrophages, insulin resistance, and glucose intolerance (20). These findings suggest that dealing with the systemic effects of Sema3E may help reduce insulin resistance. For example, mice fed a high-fat diet exhibit changes in their serum, muscle, and adipose tissue lipid profiles indicative of mitochondrial dysfunction, and incubating macrophages with these lipids drives (22, 23).

In summary, these studies support that the axis of Sema3E-Plexin D1 should be considered an essential factor in developing adipose tissue inflammation and may contribute to systemic insulin resistance and diabetes. To that end, the inhibition of the Sema3E-Plexin D1 axis reduces the inflammation of the adipose tissue significantly and improves insulin resistance in the diet-induced obese mouse model (20). Conversely, excessive expression of Sema3E in the adipose tissue is a causative factor in inflammation and insulin resistance. Nonetheless, further studies are needed to identify possible treatment opportunities for Sema3E in obesity and its role in regulating the function of immune cells and inflammatory responses.

ANIMAL TO HUMAN MODEL - EXERCISE TRAINING AND SEMAPHORIN 3E/PLEXIND1 AXIS

There are still unresolved questions regarding how we design and interpret immunometabolic changes in the animal model and successfully translate these approaches to humans to treat or prevent disease. Hotamisligil states that we must be mindful of the large inter-individual variability in the magnitude of the immune response in humans (24).

However, exercise training is influential in reducing inflammation and the subsequent risk of developing obesity, diabetes, and cardiovascular disease (25, 26). Due to these positive effects of exercise training on metabolic outcomes, we propose that exercise training may improve insulin resistance by reducing adipose tissue inflammation by inhibiting and suppressing the Sema3E-Plexin D1 axis. Future research is warranted on the effects of exercise training on Sema3E and its receptor Plexin D1. Plexin-D1/Sema3E axis is a known trigger in systemic sclerosis (SSc) endothelium but may have a role in the dysregulation of angiogenesis and vascular tone control (27). In summary, the Semaphorin 3E/PlexinD1 axis is influenced by macrophage inflammation and changes in vascular tone (27), and conversely, exercise is known to reduce endothelium dysfunction and subsequent macrophage infiltration (28).

No studies are currently detailing the possible mechanisms of exercise training and physical activity that influence the Semaphorin 3E/Plexin D1 axis in animals or humans. Relative to exercise training, depending on the type and intensity, it stimulates the secretion of various hormones such as catecholamines (29), growth hormone, and glucagon (30, 31), indirectly decreasing adipose tissue and insulin resistance. These events may result from decreased Semaphorin 3E/Plexin D1 axis level. In addition, positive changes in blood lipids (32) and those adipokines related to insulin resistance (RBP-4 and TNF-α) (32), leptin (33), visfatin (34), adiponectin (35), and omentin (36) have been observed following exercise training. They may also decrease the secretion of Semaphorin 3E/Plexin D1 axis. On the other hand, exercise training is also associated with increased antioxidant capacity and decreased free radicals (37, 38), which lead to reduced inflammation, insulin resistance, and potential obesity (39).

Several studies have reported that exercise training increases cholesterol transporters such ABCG and ABCA1 within adipose tissue, increasing cholesterol transportation and reducing adipose tissue (40, 41) and again, exerting a positive influence on Semaphorin 3E/Plexin D1 Axis levels.

Besides exercise training decreases, adipose tissue, through increasing the activity of beta-oxidation, improves the fat utilization in lipolysis (42, 43), potentially leading to improvement in both Semaphorin 3E/Plexin D1 axis levels and insulin resistance. Exercise training also enhances blood-oxygen-delivery to adipose tissue, fat-burning, fatty acids transportation, and oxidation by increasing adipose tissue's angiogenesis (44, 45). These changes are also possibly associated with improved insulin resistance and Semaphorin 3E/Plexin D1 Axis levels.

CONCLUSION

many researchers have considered the implications of manipulating immune responses to treat human metabolic diseases. However, few have

considered the approach discussed in this review. We recommend that more consideration be given to identifying the influential factors associated with semaphorins and the role physical exercise plays in these factors to improve our understanding of how inflammation affects obesity and insulin resistance.

ACKNOWLEDGMENT

N/A.

FINANCIAL DISCLOSURE

No financial support was obtained for this study.

FUNDING

This research received no external funding.

ROLE OF THE SPONSOR

There are no sponsors.

AUTHORS' CONTRIBUTION

All authors contributed to the interpretation of the data and to writing/reviewing the manuscript. All authors take final responsibility for submitting the manuscript for publication.

ARTIFICIAL INTELLIGENCE (AI) USE

The author declares no AI usage.

CONFLICT OF INTEREST

The authors declare no conflict of interest concerning the authors' contribution and article's publication.

REFERENCES

1. Hinge CR, Ingle SB, Adgaonkar BD. Body Mass Index, Blood Pressure and Lipid profile in type 2 diabetes-Review. Int J Cur Res Rev Vol. 2018;10(10):1.
2. Saklayen MG. The global epidemic of the metabolic syndrome. Current hypertension reports. 2018;20(2):12.
3. Glass CK, Olefsky JM. Inflammation and lipid signaling in the etiology of insulin resistance. Cell Metabolism. 2012;15(5):635-45.
4. Schmidt AM, Moore KJ. The Semaphorin 3E/PlexinD1 axis regulates macrophage inflammation in obesity. Cell Metabolism. 2013;18(4):461-2.
5. Saeidi A, Tayebi SM, Khosravi A, Malekian F, Khodamoradi A, Sellami M, et al. Effects of exercise training on type 2-diabetes: the role of Meteorin-like protein. Health Promot Perspect. 2019;9(2):89-91.
6. Saeidi A, Hackney AC, Tayebi SM, Ahmadian M, Zouhal H. Diabetes, Insulin Resistance, Fetuin-B and Exercise Training. Ann Appl Sport Sci. 2019;7(2):1-2.
7. Saeidi A, Tayebi SM, Khosravi A, Razi O, Sellami M, Abderrahman AB, Zouhal H. Obesity, fat mass, osteopontin and exercise training. International Journal of Applied Exercise Physiology. 2019;8(1):177-9.
8. Tayebi SM, Ghanbari-Niaki A, Saeidi A, Hackney AC. Exercise Training, Neuregulin 4 and Obesity. Ann Appl Sport Sci. 2017;5(2):1-2.
9. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Molecular and cellular endocrinology. 2010;316(2):129-39.
10. Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Frontiers in endocrinology. 2013;4.
11. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. Journal of Clinical Investigation. 2005;115(5):1111.
12. Zabel BA, Zuniga L, Ohyama T, Allen SJ, Cichy J, Handel TM, Butcher EC. Chemoattractants, extracellular proteases, and the integrated host defense response. Experimental hematology. 2006;34(8):1021-32.
13. Goralski KB, Acott PD, Fraser AD, Worth D, Sinal CJ. Brain cyclosporin A levels are determined by ontogenic regulation of mdr1a expression. Drug metabolism and disposition. 2006;34(2):288-95.
14. Wittamer V, Bondue B, Guillabert A, Vassart G, Parmentier M, Communi D. Neutrophil-mediated maturation of chemerin: a link between innate and adaptive immunity. The Journal of immunology. 2005;175(1):487-93.
15. Zemet R, Brandt B, Iskilova M, Hemi R, Marom-Haham L, Yinon Y, et al. 231: Semaphorin 3E, a novel adipokine with pro inflammatory and insulin resistance properties, is a physiologic constituent of human fetus plasma. American Journal of Obstetrics & Gynecology. 2016;214(1):S137.

16. Nishide M, Kumanogoh A. The role of semaphorins in immune responses and autoimmune rheumatic diseases. Nature Reviews Rheumatology. 2018;14(1):19.
17. Püschel AW. Semaphorins: repulsive guidance molecules show their attractive side. Nature neuroscience. 1999;2(9):777.
18. Perälä N, Sariola H, Immonen T. More than nervous: the emerging roles of plexins. Differentiation. 2012;83(1):77-91.
19. Gu C, Yoshida Y, Livet J, Reimert DV, Mann F, Merte J, et al. Semaphorin 3E and plexin-D1 control vascular pattern independently of neuropilins. Science. 2005;307(5707):265-8.
20. Shimizu I, Yoshida Y, Moriya J, Nojima A, Uemura A, Kobayashi Y, Minamino T. Semaphorin3E-induced inflammation contributes to insulin resistance in dietary obesity. Cell Metabolism. 2013;18(4):491-504.
21. Zemet R, Iskilova M, Brandt B, Hemi R, Marom-Haham L, Kanety H, Mazaki-Tovi S. 625: The intricate interface between metabolic and inflammation regulation: Placental expression of Semaphorin 3E and its receptor, PlexinD1, are associated with obesity and insulin resistance in normal pregnancy and gestational diabetes mellitus. American Journal of Obstetrics & Gynecology. 2018;218(1):S373.
22. Lim J, Iyer A, Liu L, Suen JY, Lohman R-J, Seow V, et al. Diet-induced obesity, adipose inflammation, and metabolic dysfunction correlating with PAR2 expression are attenuated by PAR2 antagonism. The FASEB Journal. 2013;27(12):4757-67.
23. Sampey BP, Freemerman AJ, Zhang J, Kuan P-F, Galanko JA, O'Connell TM, et al. Metabolomic profiling reveals mitochondrial-derived lipid biomarkers that drive obesity-associated inflammation. PloS one. 2012;7(6):e38812.
24. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177.
25. Pedersen BK. The anti-inflammatory effect of exercise: its role in diabetes and cardiovascular disease control. Essays in biochemistry. 2006;42:105-17.
26. Zouhal H, Lemoine-Morel S, Mathieu M-E, Casazza GA, Jabbour G. Catecholamines and obesity: effects of exercise and training. Sports Medicine. 2013;43(7):591-600.
27. Mazzotta C, Romano E, Bruni C, Manetti M, Lepri G, Bellando-Randone S, et al. Plexin-D1/Semaphorin 3E pathway may contribute to dysregulation of vascular tone control and defective angiogenesis in systemic sclerosis. Arthritis research & therapy. 2015;17(1):221.
28. Tenório TR, Balagopal PB, Andersen LB, Ritti-Dias RM, Hill JO, Lofrano-Prado MC, Prado WL. Effect of Low-Versus High-Intensity Exercise Training on Biomarkers of Inflammation and Endothelial Dysfunction in Adolescents With Obesity: A 6-Month Randomized Exercise Intervention Study. Pediatric exercise science. 2018;30(1):96-105.
29. Zouhal H, Jacob C, Delamarche P, Gratas-Delamarche A. Catecholamines and the effects of exercise, training and gender. Sports medicine. 2008;38(5):401-23.
30. Hackney AC, Kraemer WJ, Hooper DR. Hormonal Changes Associated with Physical Activity and Exercise Training. Exercise and Human Reproduction: Springer; 2016. p. 125-43.
31. Kindermann W, Schnabel A, Schmitt W, Biro G, Cassens J, Weber F. Catecholamines, growth hormone, cortisol, insulin, and sex hormones in anaerobic and aerobic exercise. European journal of applied physiology and occupational physiology. 1982;49(3):389-99.
32. Tayebi SM, Hasannezhad P, Saeidi A, Fadaei MR. Intense circuit resistance training along with Zataria multiflora supplementation reduced plasma retinol binding protein-4 and tumor necrosis factor-α in postmenopausal females. Jundishapur Journal of Natural Pharmaceutical Products. 2018;13(2).
33. Fedewa MV, Hathaway ED, Ward-Ritacco CL, Williams TD, Dobbs WC. The effect of chronic exercise training on leptin: a systematic review and meta-analysis of randomized controlled trials. Sports medicine. 2018;48(6):1437-50.
34. Gholami M, Abdi A, Abbasi A, Ghanbari-Niaki A. The effect of glucose intake on Plasma Visfatin response following an aerobic exercise session in male students. Hormozgan Medical Journal. 2017;20.
35. Wang X, You T, Murphy K, Lyles MF, Nicklas BJ. Addition of exercise increases plasma adiponectin and release from adipose tissue. Medicine and science in sports and exercise. 2015;47(11):2450.

36. Wilms B, Ernst B, Gerig R, Schultes B. Plasma omentin-1 levels are related to exercise performance in obese women and increase upon aerobic endurance training. Experimental and Clinical Endocrinology & Diabetes. 2015;123(03):187-92.
37. Park S-Y, Kwak Y-S. Impact of aerobic and anaerobic exercise training on oxidative stress and antioxidant defense in athletes. Journal of exercise rehabilitation. 2016;12(2):113.
38. Yavari A, Javadi M, Mirmiran P, Bahadoran Z. Exercise-induced oxidative stress and dietary antioxidants. Asian journal of sports medicine. 2015;6(1).
39. Mendelson M, Michallet AS, Monneret D, Perrin C, Estève F, Lombard P, et al. Impact of exercise training without caloric restriction on inflammation, insulin resistance and visceral fat mass in obese adolescents. Pediatric obesity. 2015;10(4):311-9.
40. Khabazian B, Niaki AG, Rahbarizadeh F, Kakhak AH, Noghabi MJ. The effect of 6 weeks of endurance training on the expression of hepatic ABCA1 in male wistar rats. World Journal of Sport Sciences. 2008;1(1):01-7.
41. Zare-Kookandeh N, Deldar H, Ghanbari-Niaki A, Ansari-Pirsaraei Z, Rahmati-Ahmadabad S, Raoof Z. ABCG1 gene responses to treadmill running with or without pistachio-atlantica in female rats. Iranian Journal of Health and Physical Activity. 2012;3(1).
42. Cornish SM, McBreairty L, Chilibeck PD, Zello GA. Fat Metabolism During Exercise and Dietary Interventions for Enhancing Fat Metabolism and Athletic Performance. Handbook of Lipids in Human Function: Elsevier; 2016. p. 499-519.
43. Flack KD, Davy BM, DeBerardinis M, Boutagy NE, McMillan RP, Hulver MW, et al. Resistance exercise training and in vitro skeletal muscle oxidative capacity in older adults. Physiological reports. 2016;4(13):e12849.
44. Corvera S, Gealekman O. Adipose tissue angiogenesis: impact on obesity and type-2 diabetes. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014;1842(3):463-72.
45. Van Pelt DW, Guth LM, Horowitz JF. Aerobic exercise elevates markers of angiogenesis and macrophage IL-6 gene expression in the subcutaneous adipose tissue of overweight-to-obese adults. Journal of Applied Physiology. 2017;123(5):1150-9.