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A GROWING JOURNEY FROM NEUROTROPHINS TO METABOTROPHINS IN CARDIOMETABOLIC DISEASES

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Abstract

Currently, obesity has been recognized as a prime risk in the development of cardiometabolic diseases (CMD) and neurodegenerative diseases (NDD). The pathogenesis and therapy of CMD are immensely complex at the cellular and molecular levels. This scenario raises the question of how such a complexity may be grappled in a more tangible manner. Since 2003, we have been thinking “what nobody has yet thought about that everybody sees”, namely, metabotrophic factors (MTF, metabotrophins). The latter include mainly (i) the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), and (ii) the adipomyokines adiponectin, irisin, BDNF, fibroblast growth factor-21 alike as adipose- and skeletal muscle-derived signaling proteins (these latter discussed in another review in the present volume of *Adipobiology*). Herein, we argue that obesity and related CMD and NDD, particularly Alzheimer's disease, may be viewed as MTF-deficient diseases. Further studies on MTF signatures and ramifications in these diseases are required. These would provide greater insights on how we can make MTF work for the improvement of physiological and psychological quality of human life.

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Introduction

Life at both the local and systemic levels requires nutritional, immune, neurotrophic and metabotrophic support. Any dysfunction or deficit in this support may lead to illness, such as obesity and related cardiometabolic diseases (CMD) such as atherosclerosis, hypertension, type 2 diabetes mellitus (T2DM), metabolic syndrome, and metabocognitive syndrome, including Alzheimer's disease (AD). At its core, obesity may be classified as dysmetabolic disorder, featured by: (i) accumulation, hypoxia and inflammation of white adipose tissue (1-4), and (ii) dysfunction of brown adipose tissue (5-9). Then, the adipose-derived proinflammatory and dysmetabolic signals are disseminated to many organs of the body. This leads to the development of CMD and neurodegenerative diseases (NDD), particularly AD, which we shall discuss in the present review as a neuro-metabolic disease.

Neurotrophins

In the 1950s at Washington University Medical School, St Louis, MO, Rita Levi-Montalcini and Stanley Cohen discovered a protein with nerve growth-stimulating effect, and they named it nerve growth factor (NGF). This *Eureka* provided a conceptual framework for the formulation of the neurotrophic hypothesis: particular neuronal types require specific trophic factors for their differentiation, function and survival (10-13).

Today, NGF and brain-derived neurotrophic factor (BDNF) and their relatives are collectively designated neurotrophins. The latter include: NGF, BDNF, neurotrophin-3 (NT-3), NT-4/5, and NT-6, also pro-NGF and pro-BDNF which are as active as their respective mature forms. Neurotrophins, particularly NGF and BDNF, were recognized as mediators of multiple biological processes, ranging from the neurotrophic (10) through immunotrophic (14) to metabotrophic effects over glucose, lipid, energy and cardiovascular homeostasis (2, 13, 15-20). Consequently, NGF and BDNF were implicated in the pathogenesis of a large spectrum of neuronal and non-neuronal diseases.

Adipose cells (adipocytes and associated cells of the white adipose tissue/WAT) also secrete various neurotrophic factors (Table 1).

Table 1. A selected list of adipose-derived neurotrophic factors (ADNF)

<p>NGF, BDNF, Glial cell line-derived neurotrophic factor Ciliary neurotrophic factor, Vascular endothelial growth factor Leptin, Adiponectin, Irisin, β-Klotho, Meteorin-like (Metrnl, also known as Cometin, Subfatin), Nprilysin (β-amyloid peptide-degrading enzyme) Fibroblast growth factor- 21, Metallothionein-I, -II, Angiopoietin-1</p>

Neurotrophins “became” metabotrophic factors and “make” CMD and AD metabotrophins-deficient diseases

In 2003 NGF-and-BDNF’s physiological profile was enlarged with one more extra-neuronal activity, namely, the improvement of metabolism of glucose and lipids, also of pancreatic beta cell and cardiovascular homeostasis. Accordingly, these neurotrophins were also named *metabotrophic factors* (MTF) or *metabotrophins*, also *metabokines* (2, 15-17, 21; from Greek *metabole*, and *trophe*, nutrition, means “nutritious for metabolism”).

The proof-of-concept was based on results demonstrating that the circulating and/or local NGF and BDNF levels are decreased in (i) human coronary atherosclerosis and in patients

with *advanced stage* of metabolic syndrome (22), (ii) T2DM (23, 24), and (iii) AD which is considered recently T3DM (25-27; for adipose AD, see 28). In contrast, the circulating levels of NGF and BDNF were significantly elevated in patients with *early stage* of metabolic syndrome (29). It remains to be elucidated whether the metabolically protective reserve of the organism is limited with the progression of metabolic syndrome.

Furthermore, circulating levels of NGF and BDNF in patients with acute coronary syndromes were measured, and they were found to be reduced significantly (30, 31). It was reported that in response to experimental stress or diabetes, NGF and BDNF levels were altered, both in white and brown adipose tissue (WAT and BAT, respectively) (32). Further, it was demonstrated that pancreatic beta cells secrete NGF and express its receptor tyrosine kinase A (TrkA^{NGF}), findings being implicated in the pathogenesis of T2DM and metabolic syndrome (33-43). Synergistically with leptin, BDNF reduces food intake (44). Accordingly, mutations of *Bdnf* gene in mice or *Ntr2k2* (encoding TrkB^{BDNF} receptor) in patients are associated with hyperphagia and severe obesity (45). Table 3 presents characteristics and a list of MTF-induced effects.

Table 3. Characteristics and effects of NGF, BDNF, and adiponectin (APN)

<p>NGF shares homology with proinsulin NGF and BDNF are produced by pancreatic beta cells and exert insulinotropic effect NGF and BDNF are trophic factors for pancreatic beta cells APN is anti-obesity, anti-diabetogenic, anti-atherogenic adipokine BDNF- and APN-deficient mice develop abnormalities similar to metabolic syndrome NGF, BDNF and APN improve cognitive processes NGF up-regulates expression of LDL receptor-related protein NGF up-regulates expression of PPAR-gamma NGF inhibits glucose-induced down-regulation of caveolin-1 NGF improves skin and corneal wound healing NGF and APN improve vascular (atheroma) wound healing NGF rescues silent myocardial ischemia in diabetes mellitus NGF improves diabetic erectile dysfunction Healthy lifestyle increases brain and/or circulating levels of NGF, BDNF, APN Atherogenic diet decreases brain BDNF levels BDNF-deficient mice develop abnormalities similar to the metabolic syndrome BDNF improves cognitive processes</p>

Table 4 shows a list of endogenous metabotrophins.

Table 4. A selected list of endogenous metabotrophins

<p>Nerve growth factor, Brain-derived neurotrophic factor Ciliary neurotrophic factor, Vascular endothelial growth factor Leptin, Adiponectin, Irisin, Fibroblast growth factor- 21, Meteorin-like (Metrl), Sirtuins (Visfatin/SIRT-2, SIRT-1), Klotho, Humanin, Omentin, Chemerin, Apelin, Otopetrin-1, Interleukin-10, Metallothionein-I,-II, Incretins (Glucagon-like peptide-1, Glucose-dependent insulinotropic polypeptide) Neuromedin-B, Kisspeptin-1, Progranulin, Kallistatin, Aquaporin-7, Angiopoietin-like protein 4</p>
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Targeting metabotrophins in drug discovery NGF and BDNF

As discussed, obesity and related CMD are featured by reduced circulating and epicardial adipose tissue levels of NGF and BDNF. Most probably, hypometabotrophinemia induces a metabolic stress, thus staying in the heart of a complex network of factors orchestrated the pathobiology of CMD. If so, drugs facilitating (boosting) the intracellular secretory pathways (46, 47) of NGF, BDNF, adiponectin, irisin as well as other MTF may represent a novel pharmacotherapeutic approach in these diseases. However, our knowledge of secretory pathways (synthesis, translocation, folding, targeting, sorting, storage, and exocytosis) of MTF remains limited.

Neurotrophins ligated two different types of receptors on the surface of neurones and other target cells: (i) high-affinity neurotrophin receptors belong to the Trk (pronounced “track”) family of tyrosine kinase receptors (TrkA, TrkB and TrkC) which bind to specific neurotrophins (e.g., TrkA^{NGF}, TrkB^{BDNF}), and (ii) low-affinity panneurotrophin receptor, p75^{NTR}, which lacks a tyrosine kinase endodomain. Hence, another approach for the discovery of novel therapeutics for obesity and its diseased relatives may indeed lie in exploring Trk^{NGF} and TrkB^{BDNF} receptor agonists (for *trackins*, see 48, 49).

As reviewed (13, 50), increasing number of reports demonstrate that damage to some tissues can be cured by the administration of NGF. For instance, (i) wounded diabetic skin, characterized by increased levels of NGF, will benefit by additional exogenous local treatment with NGF, (ii) elevated local NGF levels in experimentally-induced cardiac ischemia is improved by exogenous administration of NGF, and (iii) NGF administration in diabetic rodents promotes repair of injured pancreatic islets.

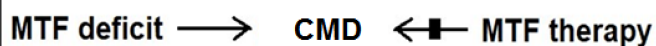
Metformin for thought or metformin 100 years latter

Metformin has its origin in the herb *Galega officinalis*, which was used for centuries to treat many diseases. In 1922, metformin (dimethylbiguanide) was synthesized, and the French physician Jean Sterne first reported the use of metformin to treat diabetes in 1957. It was demonstrated that metformin had the potential to decrease blood glucose with fewer gastrointestinal adverse effects than others drugs used for the same purpose. Today, this drug is a first-line therapy for T2DM as a monotherapy or in combination. Recent evidence suggests that metformin is a multi-therapeutic drug including its neuroprotective and procognitive actions. Observational studies of metformin-treated T2DM patients reported lower rates of dementia, reduced depressive symptoms, and a reduced risk of cognitive impairment, with the lowest risk seen in those patients with longer-term (>6 years) metformin use (51-54; also see 55, 56). Intriguingly, metformin increases brain expression of BDNF, a procognitive metabotrophin (57).

Noteworthy, (i) both brain and adipose tissue have elevated amyloid precursor protein (APP) levels in obesity, (ii) there is an extraneuronal production both of APP and amyloid β (A β) peptides, including in WAT, and (iii) the administration of streptozotocin, a well known experimental model for type 1 diabetes, induces brain insulin resistance and cognitive alterations resembling the status of AD patients (58). Hence, an intriguing question emerges: can these AD-associated molecules spread from adipose tissue to the brain? In the same stream-of-associations, a growing body of evidence suggested that metabolic syndrome (impaired glucose tolerance, abdominal obesity, hypertension, hypertriglyceridemia, and a reduced “good”, HDL cholesterol) may be important in the development of cognitive impairment, including AD. With other words, metabodegeneration may pivotally be involved in the process of neurodegeneration of AD; this may clarify approaches valuable both in preventing and therapy of the disease. Hence, new diagnostic term were proposed: „metabolic-cognitive syndrome“ (59, 60) and “T3DM” (25, 61-63).

Conclusion

Many basic and clinical studies have demonstrated that circulating and/or tissue levels of metabotrophins are reduced in individuals with obesity and related CMD. The scheme within the box below illustrates the possible involvement of metabotrophins both in the pathobiology and the therapy of CMD, including AD, viewed as metabotrophins-deficient diseases.



In this connection, Figure 1 illustrates our concept of the potential significance of MTF in the pathogenesis of CMD and NMD, particularly AD.

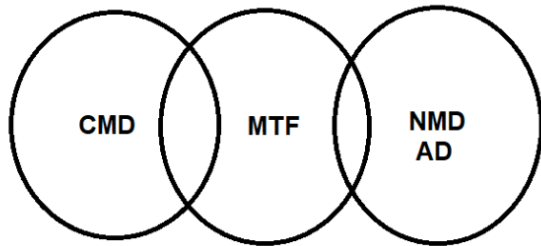


Figure 1. Metabotrophic factors (MTF) on the cross-road of cardiometabolic diseases (CMD) and neurometabolic diseases (NMD), particularly Alzheimer's disease (AD). Credit for Nikifor N. Chalidakov. From: (61, 62; also see 25, 63-65).

Since 2003 (2), we have been “thinking what nobody has yet thought about that which everybody sees” with respect to the concept of metabotrophins and their relevance for the cellular and molecular mechanisms of CMD and NMD (see also 12, 15, 16, 18, 28, 38, 58).

Yet, we have to keep in mind Robert Frost's poem *The Secret Sits*:

*We dance round in a ring and suppose,
But the Secret sits in the middle and knows.*

Future studies on metabotrophins signature in CMD and NMD, particularly AD and Parkinson's disease, may therefore cultivate a more relevant thinking about how we can make these talented biomolecules work for the improvement of physical and mental quality of life of *Homo sapiens*.

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Conflict of interest statement

The authors declare that no conflicts of interest exists.

References

1. Trayhurn P. Hypoxia and adipocyte physiology: implications for adipose tissue dysfunction in obesity. *Annu*

- Rev Nutr* 2014;34:207-36. DOI: 10.1146/annurev-nutr-071812-161156
2. Chalidakov GN, Fiore M, Hristova MG, Aloe L. Metabotrophic potential of neurotrophins: implication in obesity and related diseases? *Med Sci Monit* 2003; 9:HY19-21.
3. Chalidakov GN, Aloe L, Tonchev AB, Fiore M. From Homo obesus to Homo diabetes: Neuroadipology insight. In: Nóbrega C, Rodríguez-López R, (eds). *Molecular Mechanisms Underpinning the Development of Obesity*, Switzerland, Springer International Publishing, 2014; pp 167-178.
4. Behl S, Singh J. Adipocytes under environmental assault: Targets for obesity? In: Tappia PS *et al* (eds). *Advances in Biochemistry in Health and Disease*, Volume 19, Switzerland, Springer Nature 2020; pp 23-41.
5. Unamuno X, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest* 2018;48(9):e12997. DOI: 10.1111/eci.12997
6. Iacobellis G, Di Gioia C, Petramala L, *et al*. Brown fat expresses adiponectin in humans. *Int J Endocrinol* 2013; 126751-126751.
7. Blirando K. Epigenetic Regulation of Adipocytes Phenotype: Implication for Perivascular Adipose Tissue Contribution to Cardiometabolic Diseases. *Adipobiology* 2016; 8:21-36.
8. Sacks H, Symonds ME. Anatomical locations of human brown adipose tissue: functional relevance and implications in obesity and type 2 diabetes. *Diabetes* 2013; 62(6): 1783-1790.
9. Villarroya F, Cereijo R, Villarroya J, *et al*. Toward an Understanding of How Immune Cells Control Brown and Beige Adipobiology. *Cell Metabolism* 2018;27(5): 954-961.
10. Levi-Montalcini R. The nerve growth factor 35 years later. *Science* 1987;237(4819): 1154-1162.
11. Fiore M, Chalidakov GN, Aloe L. Nerve growth factor as a signaling molecule for nerve cells and also for the neuroendocrine-immune systems. *Rev Neurosci* 20(2): 133-145, 2009.
12. Aloe L, Tonchev A, Fiore M, Chalidakov G. Homo diabetes: involvement of metabotrophic factors. *Adipobiology* 2012;5: 45-49.
13. Rocco ML, Soligo M, Manni L, Aloe L. Nerve Growth Factor: Early Studies and Recent Clinical Trials. *Curr Neuropharmacol* 2018;16(10): 1455-1465.
14. Aloe L, Levi-Montalcini R. Mast cells increase in tissues of neonatal rats injected with the nerve growth factor. *Brain Res* 1977;133(2): 358-366.

15. Chalidakov GN, Fiore M, Tonchev AB, et al. Homo obesus: a metabotrophin-deficient species. Pharmacology and nutrition insight. *Curr Pharm Des* 2007; 13(21): 2176-2179.
16. Chalidakov G. The metabotrophic NGF and BDNF: an emerging concept. *Arch Ital Biol* 2011;149(2): 257-263.
17. Töre F, Tonchev A, Fiore M, et al. From Adipose Tissue Protein Secretion to Adipopharmacology of Disease. *Immunol Endocr Metab Agents - Med Chem* 2007; 7:149-155.
18. Yanev S, Aloe L, Fiore M, Chalidakov GN. Neurotrophic and metabotrophic potential of nerve growth factor and brain-derived neurotrophic factor: Linking cardiometabolic and neuropsychiatric diseases. *World J Pharmacol* 2013; 2(4): 92-99.
19. Rosenbaum T, Vidaltamayo R, Sánchez-Soto MC, et al. Pancreatic beta cells synthesize and secrete nerve growth factor. *Proc Nat Acad Scien USA* 1998; 95(13): 7784-7788.
20. Vidaltamayo R, Mery C, Angeles-Angeles A, et al. Expression of nerve growth factor in human pancreatic beta cells. *Growth Factors* (Switzerland) 2003; 21:103-107.
21. Sornelli F, Fiore M, Chalidakov G, Aloe L. Brain-derived neurotrophic factor: A new adipokine. *Biomed Rev* 2007; 18:85-88.
22. Chalidakov GN, Fiore M, Stankulov IS, et al. Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? *Prog Brain Res* 2004;146:279-289.
23. Krabbe KS, Nielsen AR, Krogh-Madsen R, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 2007;50(2): 431-438.
24. Yamanaka M, Itakura Y, Ono-Kishino M, et al. Intermittent administration of brain-derived neurotrophic factor (BDNF) ameliorates glucose metabolism and prevents pancreatic exhaustion in diabetic mice. *J Biosci Bioeng* 2008;105(4): 395-402.
25. de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. *J Diabetes Sci Technol* 2008;2(6): 1101-1113.
26. Dar TA, Sheikh IA, Ganie SA, et al. Molecular linkages between diabetes and Alzheimer's disease: current scenario and future prospects. *CNS Neurol Disord Drug Targets* 2014;13(2): 290-298.
27. Sridhar GR, Thota H, Allam AR, et al. Alzheimer's disease and type 2 diabetes mellitus: the cholinesterase connection? *Lipids Health Dis* 2006;5:28.
28. Aloe L, Tonchev AB, Maucher A, et al. Adipobiology of the brain: From brain diabetes to adipose Alzheimer's disease. *Adipobiology* 2015;7:37-42.
29. Hristova M. NGF and BDNF in patients with metabolic syndrome. Varna: Medical University; PhD Thesis. 2002.
30. Manni L, Nikolova V, Vyagova D, et al. Reduced plasma levels of NGF and BDNF in patients with acute coronary syndromes. *Int J Cardiol* 2005;102(1): 169-171.
31. Ejiri J, Inoue N, Kobayashi S, et al. Possible Role of Brain-Derived Neurotrophic Factor in the Pathogenesis of Coronary Artery Disease. *Circulation* 2005;112(14): 2114-2120.
32. Sornelli F, Fiore M, Chalidakov GN, Aloe L. Adipose tissue-derived nerve growth factor and brain-derived neurotrophic factor: results from experimental stress and diabetes. *Gen Physiol Biophys* 2009;28 Spec No 179-183.
33. Larrieta M, Vital P, Mendoza-Rodríguez A, et al. Nerve growth factor increases in pancreatic beta cells after streptozotocin-induced damage in rats. *Exp Biol Med (Maywood, N.J.)* 2006;231:396-402.
34. Geroldi D, Minoretto P, Emanuele E. Brain-derived neurotrophic factor and the metabolic syndrome: more than just a hypothesis. *Med Hypotheses* 2006;67(1): 195-196.
35. Schulte-Herbrüggen O, Braun A, Wronski S, et al. Neurotrophic Factors-A Tool for Therapeutic Strategies in Neurological, Neuropsychiatric and Neuroimmunological Diseases? *Curr Med Chem* 2007; 14(2318-2329).
36. Pedersen BK, Pedersen M, Krabbe KS, et al. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. *Exp Physiol* 2009;94(12): 1153-1160.
37. Bariohay B, Lebrun B, Moyse E, Jean A. Brain-Derived Neurotrophic Factor Plays a Role as an Anorexigenic Factor in the Dorsal Vagal Complex. *Endocrinology* 2005;146(12): 5612-5620.
38. Gomez-Pinilla F, Vaynman S, Ying Z. Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. *Eur J Neurosci* 2008; 28(11): 2278-2287.
39. Aloe L, Tirassa P, Lambiase A. The topical application of nerve growth factor as a pharmacological tool for human corneal and skin ulcers. *Pharmacol Res* 57(4): 2008;253-258.
40. Karatzas A, Katsanos K, Lilis I, et al. NGF Promotes Hemodynamic Recovery in a Rabbit Hindlimb Ischemic Model Through trkA- and VEGFR2-dependent Pathways. *J Cardiovasc Pharmacol* 2013;62(3): 270-277.
41. Meek TH, Wisse BE, Thaler JP, et al. BDNF action in the brain attenuates diabetic hyperglycemia via insulin-independent inhibition of hepatic glucose production. *Diabetes* 2013;62(5): 1512-1518.

42. Rao AA. Views and opinion on BDNF as a target for diabetic cognitive dysfunction. *Bioinformation* 2013; 9(11): 551-554.
43. Lebrun B, Bariohay B, Moyse E, Jean A. Brain-derived neurotrophic factor (BDNF) and food intake regulation: A minireview. *Auton Neurosci* 2006;127:30-38.
44. Nicholson JR, Peter J-C, Lecourt A-C, *et al.* Melanocortin-4 Receptor Activation Stimulates Hypothalamic Brain-Derived Neurotrophic Factor Release to Regulate Food Intake, Body Temperature and Cardiovascular Function. *J Neuroendocrinol* 2007;19(12): 974-982.
45. Fujinami A, Ohta K, Obayashi H, *et al.* Serum brain-derived neurotrophic factor in patients with type 2 diabetes mellitus: Relationship to glucose metabolism and biomarkers of insulin resistance. *Clin Biochem* 41(10): 812-817, 2008.
46. Yamanaka M, Itakura Y, Tsuchida A, *et al.* Comparison of the antidiabetic effects of brain-derived neurotrophic factor and thiazolidinediones in obese diabetic mice. *Diabet Obes Metab* 2007; 9(6): 879-888.
47. Chaldakov GN, Vankov VN. Morphological aspects of secretion in the arterial smooth muscle cell, with special reference to the golgi complex and microtubular cytoskeleton. *Atherosclerosis* 1986;61(3): 175-192.
48. Chaldakov G. Human Body as a Multicrine System, with Special Reference to Cell Protein Secretion: From Vascular Smooth Muscles to Adipose Tissue. *Biomed Rev* 2016;27(VIII-XIX).
49. Yanev S, Fiore M, Hinev A, *et al.* From Antitubulins to Trackins. *Biomed Rev* 2017;27:45-53.
50. Carito V, Venditti A, Bianco A, *et al.* Effects of olive leaf polyphenols on male mouse brain NGF, BDNF and their receptors TrkA, TrkB and p75. *Natural Product Res* 2014;28(22): 1970-1984.
51. Rotermund C, Machtetanz G, Fitzgerald JC. The therapeutic potential of metformin in neurodegenerative diseases. *Front Endocrinol* 2018; 9: 400.
52. Cheng C, Lin CH, Tsai YW, Tsai CJ, Chou PH, Lan TH. Type 2 diabetes and antidiabetic medications in relation to dementia diagnosis. *J Gerontol Ser A Biol Sci Med Sci* 2014; 69: 1299–1305.
53. Guo M, Mi J, Jiang QM, Xu JM, Tang YY, Tian G, *et al.* Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. *Clin Exp Pharmacol Physiol* 2014, 41, 650–656.
54. Ng TP, Feng L, Yap KB, Lee TS, Tan CH, Winblad B. Long-term metformin usage and cognitive function among older adults with diabetes. *J Alzheimer's Dis* 2014, 41, 61–68.
55. El Massry M, Alaeddine LM, Ali L, Saad C, Eid AA. Metformin: A growing journey from glycemic control to the treatment of Alzheimer's disease and depression. *Curr Med Chem* 2021;28(12):2328-2345. DOI: 10.2174/0929867327666200908114902
56. Cardoso S, Moreira PI. Antidiabetic drugs for Alzheimer's and Parkinson's diseases: Repurposing insulin, metformin, and thiazolidinediones. *Int Rev Neurobiol* 2020;155:37-64. DOI: 10.1016/bs.irn.2020.02.010
57. Muñoz-Arenas G, Pulido G, Treviño S, Vázquez-Roque R, Flores G, *et al.* Effects of metformin on recognition memory and hippocampal neuroplasticity in rats with metabolic syndrome. *Synapse* 2020;74(9):e22153. DOI: 10.1002/syn.22153
58. Lester-Coll N, Rivera EJ, Soscia SJ, *et al.* Intracerebral streptozotocin model of type 3 diabetes: Relevance to sporadic Alzheimer's disease. *J Alzheimer's Dis* 2006;9:13-33.
59. Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarolo D, *et al.* Metabolic-Cognitive Syndrome: A Cross-talk between Metabolic Syndrome and Alzheimer's Disease. *Ageing Res Rev* 2010;
60. Giordano V, Peluso G, Iannuccelli M, Benatti P, Nicolai R, Calvani M. Systemic and brain metabolic dysfunction as a new paradigm for approaching Alzheimer's dementia. *Neurochem Res* 2007;32:555-567.
61. Frohlich J, Chaldakov GN, Vinciguerra M. Cardio- and neurometabolic adipobiology: Consequences and implications for therapy. *Int J Mol Sci* 2021; 22(8): 4137. DOI:10.3390/ijms22084137
62. Chaldakov GN, Aloe A, Rancic G, Pancheva RZ, Hiriart M, Fiore M, Yanev S. Chapter 16. The Relevance of Metabotrophic Factors in Pathobiology and Therapy of Obesity and Related Diseases. In: P.S. Tappia *et al.* (eds.), *Cellular and Biochemical Mechanisms of Obesity, Advances in Biochemistry in Health and Disease* 23. Springer Nature Switzerland AG 2021. DOI:10.1007/978-3-030-84763-0_16
63. Lee Y-H, Tharp WG, Maple RL, *et al.* Amyloid Precursor Protein Expression Is Upregulated in Adipocytes in Obesity. *Obesity* 2008;16(7): 1493-1500.
64. Katsuda T, Tsuchiya R, Kosaka N, *et al.* Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. *Sci Rep* 2013;3:1197.
65. Raine L, Drollette E, Kao S-C, Westfall D, Chaddock-Heyman L, Kramer AF, *et al.* The associations between adiposity, cognitive function, and achievement in children. *Med Sci Sports Exerc* 2-18;. 50 (9): 1868–1874.
66. Lucci B. The contribution of Gaetano Perusini to the definition of Alzheimer's disease. *Ital J Neurol Sci* 1998;19:49-52.