Adipobiology
ISSN 1313-3705

DANCE ROUND

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

THE ADIPOSE TISSUE: A NEW MEMBER OF THE DIFFUSE NEUROENDOCRINE SYSTEM?

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Abstract

Adipose tissue is a sophisticated module, consisting of adipocytes and non-adipocyte cellular elements including stromal, vascular, nerve and immune cells. There is at present evidence that sharing of ligands and their receptors constitutes a molecular language of the human's body, which is also the case for adipose tissue and hypothalamus-pituitary gland. Historically, Nikolai Kulchitsky's identification of the enterochromaffin cell in 1897 formed the basis for the subsequent delineation of the diffuse neuroendocrine system (DNES) by Friedrich Feyrter in 1938. In DNES paradigm, the secretion of hormones, neuropeptides and neurotrophic factors is executed by cells disseminated throughout the body, for example, Kulchitsky (enterochromaffin) cells, testicular Leydig cells, and hepatic stellate cells. Here we propose that the adipose tissue might be a new member of DNES. Today (*dnes*, in Bulgarian), adipose tissue is "getting nervous" indeed: (*i*) synthesizes neuropeptides, neurotrophic factors, neurotransmitters, hypothalamic hormones/releasing factors and their receptors, (*ii*) like brain expresses endocannabinoids and amyloid precursor protein and, for steroidogenesis, the enzyme aromatase (P450arom), (*iii*) adipocytes may originate from the neural crest cells, and (*iv*) adipose-derived stem cells may differentiate into neuronal cells. Further molecular profiling of adipose tissue may provide new biological insights on its neuroendocrine potential. Overall this may frame a novel field of study, neuroadipobiology; its development and clinical application may contribute to the improvement of human's health.

Adipobiology 2009; 1:87-93

Key words: adipose tissue, brain, hormones, neuropeptides, neurotrophic factors, neurotransmitters

Received 27 July 2009, accepted 25 August 2009.
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Adipose tissue

In the last 20 years, the physical, mental and economic burden of obesity and related diseases is reaching pandemic proportions. Arguably, we have learned more about the molecular control of food intake and energy homeostasis. It is an intricate feedback system in which food intake and energy expenditure are balanced through brain-adipose, brain-gut, entero-insular and reward circuits.

White and brown adipose tissue (WAT and BAT) are morphological and functional expressions of a dynamic system, consisting of adipocytes and non-adipocyte cellular elements, including stromal, vascular, nerve and immune cells (1). Adipose tissue ("WAT" will be assumed from hereon) also contains cells that have the ability to differentiate into several lineages including neuronal cells. By sending and receiving different types of protein and non-protein signals, adipose tissue communicates via

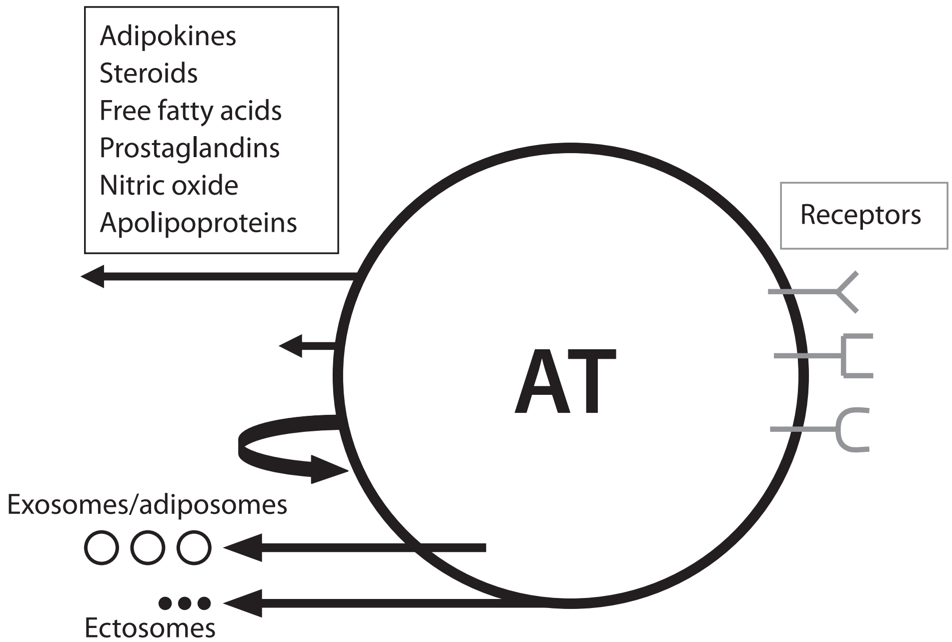

Figure 1. A drawing illustrating both secretory and receptive nature of adipose tissue (AT). At secretory level, AT-derived signaling molecules communicate via multiple pathways such as endocrine (arrows 1,4,5, from up-down), paracrine (arrow 2) and autocrine (arrow 3, curved) as well as via exosomes (multivesicular body-derived microvessels) and ectosomes (plasma membrane-shedding microparticles) (see references 5,89; for exosomes/adiposomes, see 90). At receptive level, AT possesses receptors for various ligands. Modified from 63.

endo- and paracrine way with many organs in the body (Fig. 1). In effect, brain-adipose network plays a pivotal role in the regulation of food intake and energy balance (2) as well as hypothalamic-pituitary cells produce "adipotrophins" (see below). It is increasingly recognized that adipose tissue expresses not only metabolic, but also secretory phenotype, synthesizing and releasing more than 100 signaling proteins designated adipokines (2-5). These are implicated in the regulation of energy, lipid and glucose homeostasis, inflammation, immunity and vascular tone as well as the pathogenesis of cardiometabolic and neurodegenerative diseases.

Neuroendocrinology of adipose tissue

While numerous studies have demonstrated that brain can control adipose tissue functions, it is only now becoming apparent that the control is bidirectional, that is, the adipose tissue can control brain neuroendocrine functions. For instance, (*i*) many neuropeptides and neurotrophic factors and their receptors are shared by the adipose tissue and brain (2-9), (*ii*) the adipokines leptin, adiponectin, resistin and fasting-induced adipose factor (angiopoietin-like protein 4) and their receptors are expressed in the brain (10-15), (*iii*) a subset of adipocytes may originate from the neural crest cells (16), and (*iv*) in cocultures of 3T3-L1 adipocytes with neurons, adipocyte-derived apolipoproteins enhance neuritogenesis and synaptogenesis (17).

Vice versa, adipose tissue produces (*i*) neuropeptide tyrosine (NPY), substance P, calcitonin gene-related protein and other neuropeptides (18-25), and (*ii*) glutamate and gamma-aminobutyric acid (GABA) neurotransmitters, N-methyl-D-aspartate (NMDA) and GABA receptors, and vesicular glutamate transporters (26,27). Moreover, macrophages, mast cells and other immune cells associate with both adipose tissue (3) and pituitary gland (28).

Further, most pituitary hormones and hypothalamic releasing factors, termed "adipotrophins" (29), express their receptors in adipose tissue, creating hypothalamic-pituitary-adipose axis (29,30) as well as some hypothalamic releasing factors are produced by adipose tissue (31,32); recently, pineal-adipose network is also appreciated (see Rančić *et al*' s abstract in this volume of *Adipobiology*). Also, various neurotrophic factors including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), vascular endothelial growth factor, insulin-like growth factor, and angiopoietin are synthesized and released from adipose tissue (20,25,33-37).

While NGF was first discovered by Rita Levi-Montalcini in 1951 as nerve growth stimulating protein produced in largest amount by the mouse submandibular glands (38), it appears today that the adipose tissue may also be a major biological source of NGF and other neurotrophic factors (reviewed in 39,40).

Noteworthy, semaphorin (Sema3A) and its receptor neuropilin-1 (41), and pantophysin, a protein related to the neuroendocrine-specific synaptophysin (42), are expressed in adipose tissue as well as neural and glial markers in neurally differentiated adipose-derived stromal cells (43-45).

Another neuroendocrine feature of adipose tissue might be its own production of both steroids and endocannabinoids. There is at present clear evidence that adipose tissue, like brain and its aromatase (P450arom) and neurosteroids, produces adiposteroids (see 3,46; the term "adiposteroids" has been introduced by Masuzaki H *et al* in 2004). Endocannabinoids and their receptors, recently extensively studied in food intake control and reward phenomena, are expressed in both hypothalamus/pituitary gland and adipose tissue (47).

Last but not least, it has been recently disclosed a metabolic paradigm for Alzheimer's disease pathogenesis including the role of obesity, cholesterol and adipokines in neurodegeneration (48-50). Also, it is increasingly clear that the hypothalamus is not the only site of leptin action, nor food intake is the only biological effect of leptin. Rather, leptin is a pleiotropic adipokine that supports learning and memory and has neurotrophic activity (14,15,51-53; also Arieh Gertler in this volume of *Adipobiology*; for apelin, a new adipokine, see 54,55). Other neurotrophic factors produced by adipose tissue (20,25,33-37,39,40) may also contribute to neuroprotection in various neuropsychiatric diseases (reviewed in 56).

From enterochromaffin cells to adipose tissue

Historically, Nikolai Konstantinovich Kulchitsky (1856-1925) has identified the enterochromaffin cells found in the crypts of Lieberkuhn of gastrointenstinal mucosa, in 1897. This discovery formed the basis for the subsequent delineation of the diffuse neuroendocrine system (DNES) by Friedrich Feyrter in 1938 (reviewed in 57,58); examples of DNES include Feyrter's Hellen Zellen (clear cells) in pancreas and gut, testicular Leydig cells (59), hepatic stellate cells (Ito cells) (60) and other cells disseminated throughout the body..

Dancing around the accumulating evidence of synthesis and release of multiple neuronal and neuroendrocrine factors and expression of their receptors and various neural markers (Table 1-3), we propose that adipose tissue might be a new member of DNES.

Today (*dnes*, in Bulgarian, Serbian, Polish and Slovak), adipose tissue is "getting nervous" indeed (61). Metaphorically, this talented tissue is increasing dramatically its intelligence quotient (IQ) (62). As well as the gut is considered a second brain (58), the adipose tissue may likely function as a third brain (63). Although "absence of proofs is not proof of absence", further neuroendocrine profiling of adipose tissue is required. It may provide new biological insights on some "newcomers" such as NGF, BDNF, CNTF, nitric oxide (64, also Tunçel *et al* in this vol-

Table 1.
Neuronal and neuroendocrine factors in adipose tissue

Neuropeptides
Agouti protein (2-5)*
Neuropeptide tyrosine (NPY) (20,25)
Calcitonin gene-related peptide (18)
Adrenomedullin (18)
Somatostatin (19)
Insulin-like growth factor (20)
Substance P (21)
Kisspeptin (22)
Neuromedin B (23)
Neurotensin (24)
Mineralocorticoid-releasing factors (31)
Corticotropin-releasing hormone (CRH) (32)
Stresscopin and urocortin (CRH-like peptides) (32)
Apelin (54; cf. 55)
Nesfatin-1 (67)
Neurotrophic factors
Leptin (2-5; cf. 15,51-53)
Apolipoprotein D, E3 (17)
Nerve growth factor (20,25,33,36)
Brain-derived neurotrophic factor (34,35,88)
Angiopoietin-1 (37)
Vascular endothelial growth factor (39)
Ciliary neurotrophic factor (20,39)
Glial cell line-derived neurotrophic factor (39,88)
Steroids (3,46; cf.81-83)
Metallothioneins (65, cf. 66)
Neurotransmitters
Noradrenaline (1)
Glutamate (26)
Gamma-aminobutyric acid (GABA) (26)

* References are indicated in parentheses.

Table 2.
Neuronal and neuroendocrine receptors in adipose tissue

Leptin (ObRb) (4)*
NPY1R, NPY2R, NPY4R (20)
Beta3-adrenergic receptor (25,64)
α2 GABAAR, NR1 NMDAR, GluR2/3 AMPAR** (26,27)
FSH, LH, ACTH, TSH, GH (29,30)
Prolactin, oxytocin, vasopressin (29,30)
p75 neurotrophin receptor (p75NTR) (33,45)
Tropomyosin-related kinase/tyrosine kinase A (Trk A) (43)
Orexin-A, -B (69)
Acetylcholine (muscarinic M3) (70)
Melatonin (84)
Melanocortin-4 receptor (85)

* References are indicated in parentheses.
****** Recent data suggests that glutamate might have neurotrophic effects, while neurotrophins, particularly BDNF, might act as neurotransmitters exerting fast modulating effects on synaptic structure and function (77). AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors of glutamate. Neuronal activation induced via small doses of AMPAR agonists, known as ampakines, has been shown to markedly raise the BDNF levels and lead to cognitive enhancement (78,79).

Table 3.
Neural and neuroendocrine markers in adipose tissue

Semaphorin (Sema3A) (41)*
Neuropilin-1 (41)
Pantophysin (42)
Neuronal nuclear antigen (43)
Nestin (43,44)
Neuron-specific enolase (43,44)
Glial fibrillary acidic protein (43,44)
Vimentin (43)
Stathmin-like 2 (71)
NF70, S100 (72,73)
c-kit (74, cf. 75)
Acetylcholinesterase and choline acetyltransferase (76)
Musashi-1 genes (80)
Amyloid precursor protein/Abeta peptides (86,87)
Beta3 tubulin (88)

* References are indicated in parentheses

ume of *Adipobiology*), metallothioneins (65, cf. 66), neuropeptides B and W and nesfatin-1 (67), and the anti-aging protein klotho (68). Onwards, this may open a novel field of research, neuroadipobiology. Systems biology approach integrating neuroendocrinology, neuroimmunology and neuroadipobiology may indeed contribute to the improvement of human's health and longevity.

Conclusion

In 1999 Albee Messing published in *Hepatology* (volume 29, pp 602-603) Editorial entitled "Nestin in the Liver – Lessons from the Brain". He wrote: "Most neuroscientists manage to get through each day without thinking of the liver even once… but I think that is about to change." This may also be the case for adipose tissue.

Acknowledgments

The authors thank Professor Michail S. Davidoff (Hamburg, Germany), Dr Danko Georgiev (Kanazawa, Japan), Dr Kamen Valchanov (Cambridge, UK) and Dr Desislav B. Kaplamadzhiev (Kanazawa, Japan) for creative reading of the manuscript.

References

1. Cinti S. Transdifferentiation properties of adipocytes in the adipose organ. *Am J Physiol Endocrinol Metab* 2009. doi:10.1152/ajpendo.00183.2009
2. Trayhurn P, Bing C, Wood IS. Adipose tissue and adipokines – energy regulation from the human perspective. *J Nutr* 2006; 136 (7 Suppl): 1935S-1939S.
3. Chaldakov GN, Stankulov IS, Hristova M, Ghenev PI. Adipobiology of disease: adipokines and adipokine-targeted pharmacology. *Curr Pharm Des* 2003; 9:1023-1031.
4. Fantuzzi G, Mazzone T, editors. *Nutrition and Health: Adipose Tissue and Adipokines in Health and Disease*. Humana Press Inc., Tokowa, NJ. 2007.
5. Renes J, Rosenow A, Mariman E. Novel adipocyte features discovered by adipoproteomics. *Adipobiology* 2009; 1: 7-18.
6. Tonchev AB, Boneva NB, Kaplamadzhiev DB, Kikuchi M, Mori Y, Sahara S, *et al*. Expression of neurotrophin receptors by proliferating glia in postischemic hippocampal CA1 sector of adult monkeys. *J Neuroimmunol* 2008; 205:20-24.
7. Wang C, Bomberg E, Billington C, Levine A, Kotz CM. Brain-derived neurotrophic factor in the hypothalamic paraventricular nucleus increases energy expenditure by elevating metabolic rate. *Am J Physiol Regul Integr Comp Physiol* 2007; 293: R992-1002.
8. Coope A, Milanski M, Araújo EP, *et al*. AdipoR1 mediates the anorexigenic and insulin/leptin-like actions of adiponectin in the hypothalamus. *FEBS Lett* 2008; 582: 1471-1476.

9. Stoyanova II, Rutten WLC, le Feber J. Orexin-A and orexin-B during the postnatal development of the rat brain. *Cell Mol Neurobiol* 2009. doi 10.1007/s10571-009-9433-z
10. Brown R, Thompson HJ, Imran SA, Ur E, Wilkinson M. Traumatic brain injury induces adipokine gene expression in rat brain. *Neurosci Lett* 2008; 432: 73-78.
11. Brown R, Imran SA, Belsham DD, Ur E, Wilkinson M. Adipokine gene expression in a novel hypothalamic neuronal cell line: resistin-dependent regulation of fasting-induced adipose factor and SOCS-3. *Neuroendocrinology* 2007; 85:232-241.
12. Brown R, Imran SA, Ur E, Wilkinson M. Valproic acid and CEBPalpha-mediated regulation of adipokine gene expression in hypothalamic neurons and 3T3-L1 adipocytes. *Neuroendocrinology* 2008; 88: 25-34.
13. Brown R, Imran SA, Wilkinson M. Lipopolysaccharide (LPS) stimulates adipokine and socs3 gene expression in mouse brain and pituitary gland in vivo, and in N-1 hypothalamic neurons in vitro. *J Neuroimmunol* 2009; 209: 96-103.
14. Bouret SG, Draper SJ, Simerly RB. Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science* 2004; 304: 108–110.
15. Scott MM, Lachey JL, Sternson SM, Lee CE, Elias CF, Friedman JM, *et al*. Leptin targets in the mouse brain. *J Comp Neurol* 2009; 514: 518-532.
16. Billon N, Monteiro MC, Dani C. Developmental origin of adipocytes: new insights into a pending question. *Biol Cell* 2008; 100:563-575.
17. Kosacka J, Gericke M, Nowicki M, Kacza J, Borlak J, Spanel-Borowski K. Apolipoproteins D and E3 exert neurotrophic and synaptogenic effects in dorsal root ganglion cell cultures. *Neuroscience* 2009; 162:282-291.
18. Gupta P, Harte AL, da Silva NF, *et al*. Expression of calcitonin gene-related peptide, adrenomedullin, and receptor modifying proteins in human adipose tissue and alteration in their expression with menopause status. *Menopause* 2007; 14: 1031-1038.
19. Seboek D, Linscheid P, Zulewski H, *et al*. Somatostatin is expressed and secreted by human adipose tissue upon infection and inflammation. *J Clin Endocrinol Metab* 2004; 89: 4833-4839.
20. Hausman GJ, Barb CR, Dean RG. Patterns of gene expression in pig adipose tissue: Insulin-like growth factor system proteins, neuropeptide Y (NPY), NPY receptors, neurotrophic factors and other secreted factors. *Domest Anim Endocrinol* 2008; 35: 24-34.
21. Karagiannides I, Pothoulakis C. Substance P, obesity, and gut inflammation. *Curr Opin Endocrinol Diabetes Obes* 2009; 16: 47-52.
22. Brown RE, Imran SA, Ur E, Wilkinson M. KiSS-1 mRNA in adipose tissue is regulated by sex hormones and food intake. *Mol Cell Endocrinol* 2008; 281:64-72.
23. Hoggard N, Bashir S, Cruickshank M, Miller JD, Speakman JR. Expression of neuromedin B in adipose tissue and its regulation by changes in energy balance. *J Mol Endocrinol* 2007; 39: 199-210.
24. Koon HW, Kim YS, Xu H, *et al*. Neurotensin induces IL-6 secretion in mouse preadipocytes and adipose tissues during 2,4,6,-trinitrobenzensulphonic acid-induced colitis. *Proc Natl Acad Sci USA* 2009;106: 8766-8771.
25. Manneràs L, Cajander S, Lönn M, Stener-Victorin E. Acupuncture and exercise restore adipose tissue expression of sympathetic markers and improve ovarian morphology in rats with dihydrotestosterone-induced PCOS. *Am J Physiol Regul Integr Comp Physiol* 2009; 296: R1124-1131.
26. Nicolaysen A, Gammelsaeter R, Storm-Mathisen J, Gundersen V, Iversen PO. The components required for amino acid neurotransmitter signaling are present in adipose tissue. *J Lipid Res* 2007; 48: 2123-2132.
27. Kulikov AV, Rzhaninova AA, Goldshtein DV, Boldyrev AA. Expression of NMDA receptors in multipotent stromal cells of human adipose tissue under conditions of retinoic acid-induced differentiation. *Bull Exp Biol Med* 2007; 144: 626-629.
28. Hoek A, Allaerts W, Leenen PJM, Schoemaker J, Drexhage HA. Dendritic cells and macrophages in the pituitary and the gonads. Evidence for their role in the fine regulation of the reproductive endocrine response. *Eur J Endocrinol* 1997; 136:8-24.
29. Schäffler A, Schölmerich J, Buechler C. The role of "adipotrophins" and the clinical importance of a potential hypothalamic-pituitary-adipose axis. *Nat Clin Pract Endocrinol Metab* 2006; 2: 374-383.
30. Schäffler A, Schölmerich J, Buechler C. Hypothesis paper. Brain talks with fat – evidence for a hypothalamic-pituitary-adipose axis? *Neuropeptides* 2005; 39: 363-367.
31. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, *et al*. Human adipocytes secrete mineralocorticoid-releasing factors. *Proc Natl Acad Sci USA* 2003; 100: 14211-14216.
32. Seres J, Bornstein SR, Seres P, *et al*. Corticotropin-releasing hormone system in human adipose tissue. *J Clin Endocrinol Metab* 2004; 89: 965-970.
33. Chaldakov 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.
34. Sornelli F, Fiore M, Chaldakov GN, Aloe L. Brain-dervied neurotrophic factor: a new adipokine. *Biomed Rev* 2007; 18: 85-88.
35. Zhao L, Wei X, Ma Z, Feng D, Tu P, Johnstone BH, *et al*. Adipose stromal cells-conditional medium protected glutamate-induced CGNs neuronal death by BDNF. *Neurosci Lett* 2009; 452: 238-240.

36. Hansen-Algenstaedt N, Algenstaedt P, Schaefer C, et al. Neural driven angiogenesis by overexpression of nerve growth factor. *Histochem Cell Biol* 2006; 125: 637-649.
37. Kosacka J, Nowicki M, Kacza J, Borlak J, Engele J, Spanel-Borowski K. Adipocyte-derived angiopoietin-1 supports neurite outgrowth and synaptogenesis of sensory neurons. *J Neurosci Res* 2006; 83: 1160-1169.
38. Levi-Montalcini R. The nerve growth factors 35 years later. *Science* 1987; 237: 1154-1162.
39. Chaldakov GN, Tonchev AB, Fiore M, Hristova MG, Pancheva R, Rancic G, *et al*. Implications for the future of obesity management. In: G Frühbeck, editor. *Peptides in Energy Balance and Obesity*. CAB International 2009; 369-389.
40. Fiore M, Chaldakov GN, Aloe L. Nerve growth factor as a signaling molecule for nerve cells and also for the neuroendocrine-immune systems. *Rev Neurosci* 2009; 20: 133-145.
41. Giordano A, Cesari P, Capparuccia L, Castellucci M, Cinti S. Sema3A and neuropilin-1 expression and distribution in rat white adipose tissue. *J Neurocytol* 2003; 32: 345-352.
42. Brooks CC, Scherer PE, Cleveland K, Whittemore JL, Lodish HF, Cheatham B. Pantophysin is a phosphoprotein component of adipocyte transport vesicles and associates with GLUT4-containing vesicles. *J Biol Chem* 2000; 275: 2029-2036.
43. Dhar S, Yoon ES, Kachgal S, Evans GR. Long-term maintenance of neuronally differentiated human adipose tissue-derived stem cells. *Tissue Eng* 2007; 13: 2625-2632.
44. Gimble JM, Guilak F, Nuttall ME, Sathishkumar S, Vidal M, Bunnell BA. In vitro differentiation potential of mesenchymal stem cells. *Transfus Med Hemother* 2008;35: 228–238.
45. Yamamoto N, Akamatsu H, Hasegawa S, *et al*. Isolation of multipotent stem cells from mouse adipose tissue. *J Dermatol Soc* 2007;48:43-52.
46. Blouin K, Veilleux A, Luu-The V, Tchernof A. Androgen metabolism in adipose tissue: recent advances. *Mol Cell Endocrinol* 2009; 301:97-103.
47. Matias I. The EC system in the adipose tissue and endocrine pancreas. In: J-P Després, V Di Marzo, editors. *Abdominal Obesity and the Endocannabinoid System. From Basic Aspects to Clinical Management of Related Cardiometabolic Risk*. Informa Healthcare USA, Inc.2009; 153-162.
48. Blass JP. A new approach to treating Alzheimer's disease. *Ann NY Acad Sci* 2008; 1147: 122-128.
49. 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.
50. Manning S. Diabetes and dementia: a common link or coincidental coexistence? *Biomed Rev* 2007;18: 59-64.
51. Zhang F, Chen J. Leptin protects hippocampal CA1 neurons against ischemic injury. *J Neurochem* 2008; 107: 578-587.
52. Morrison CD. Leptin signaling in brain: A link between nutrition and cognition? *Biochim Biophys Acta* 2009; 1792: 401-408.
53. Tezapsidis N, Johnston JM, Smith MA, Ashford JW, Casadesus G, Robakis NK, *et al*. Leptin: a novel therapeutic strategy for Alzheimer's disease. *J Alzheimers Dis* 2009; 16: 731-740.
54. Bełtowski J. Apelin and visfatin: unique "beneficial" adipokines upregulated in obesity? *Med Sci Monit* 2006; 12: RA112-119.
55. Reaux A, De Mota N, Skultetyova I, Lenkei Z, El Messari S, Gallatz K, *et al*. Physiological role of a novel neuropeptide, apelin, and its receptor in the rat brain. *J Neurochem* 2001; 77: 1085-1096.
56. Chaldakov GN, Tonchev AB, Aloe L. NGF and BDNF: from nerves to adipose tissue, from neurokines to metabokines. *Rivista Psichiatr* 2009; 44: 79-87.
57. Drozdov I, Modlin IM, Kidd M, Goloubinov VV. From Leningrad to London: the saga of Kulchitsky and the legacy of the enterochromaffin cell. *Neuroendocrinology* 2009; 89: 1-12. 58. Small CJ, Wynne K, Bloom SR. The gut as a second brain. In: G Frühbeck, editor. *Peptides in Energy Balance and Obesity*. CAB International. 2009; 93-113.
59. Davidoff MS, Schulze W, Middendorff R, Holstein AF. The Leydig cell of the human testis - a new member of the diffuse neuroendocrine system. *Cell Tissue Res* 1993; 271: 429-439.
60. Roskams T, Cassiman D, De Vos R, Libbrecht L. Neuroregulation of the neuroendocrine compartment of the liver. *Anat Rec A Discov Mol Cell Evol Biol* 2004;280:910-923.
61. Fliers E, Kreier F, Voshol PJ, Havekes LM, Sauerwein HP, Kalsbeek A, *et al*. White adipose tissue: getting nervous. *J Neuroendocrinol* 2003; 15: 1005-1010.
62. Chaldakov GN, Fiore M, Tonchev AB, Hristova MG, Nikolova V, Aloe L. Tissue with high IQ: adipose-derived stem cells in neural regeneration. *Neural Regen Res* 2009; in print.
63. Chaldakov GN, Fiore M, Tonchev AB, Hristova MG, Ranĉić G, Aloe L. The adipose tissue as a third brain. *Obesity Metab* 2009; in print.
64. Canová NK, Lincová D, Kmonícková E, Kameníková L, Farghali H. Nitric oxide production from rat adipocytes is modulated by beta3-adrenergic receptor agonists and is involved in a cyclic AMP-dependent lipolysis in adipocytes. *Nitric Oxide* 2006; 14: 200-211.
65. Do MS, Nam SY, Hong SE, Kim KW, Duncan JS, Beattie JH, *et al*. Metallothionein gene expression in human adipose tissue from lean and obese subjects. *Horm Metab Res* 2002; 34:348-351.
66. Pedersen MO, Jensen R, Pedersen DS, Penkowa M, *et al*. Metallothionein-I+II in neuroprotection. *Biofactors* 2009; 35:315-325.

67. Harrold JA, Williams G. Newcomers and supporting actors. In: G Frühbeck, editor. *Peptides in Energy Balance and Obesity*. CAB International. 2009; 61-92.
68. Chihara Y, Rakugi H, Ishikawa K, Ikushima M, Maekawa Y, Ohta J, *et al*. Klotho protein promotes adipocyte differentiation. *Endocrinology* 2006;147:3835-3842.
69. Digby JE, Chen J, Tang JY, Lehnert H, Matthews RN, Randeva HS. Orexin receptor expression in human adipose tissue: effects of orexin-A and orexin-B. *J Endocrinol* 2006; 191: 129-136.
70. Yang TT, Chang CK, Tsao CW, Hsu YM, Hsu CT, Cheng JT. Activation of muscarinic M-3 receptor may decrease glucose uptake and lipolysis in adipose tissue of rats. *Neurosci Lett* 2009; 451: 57-59.
71. Chiellini C, Grenningloh G, Cochet O, Scheideler M, Trajanoski Z, Ailhaud G, *et al*. Stathmin-like 2, a developmentally-associated neuronal marker, is expressed and modulated during osteogenesis of human mesenchymal stem cells. *Biochem Biophys Res Commun* 2008; 374: 64-68.
72. Ning H, Lin G, Lue TF, Lin CS. Neuron-like differentiation of adipose tissue-derived stromal cells and vascular smooth muscle cells. *Differentiation* 2006; 74:510-518.
73. Atanassova P. Immunohistochemical expression of S-100 protein in human embryonal fat cells. *Cells Tissues Organs* 2001; 169:355-360.
74. Bai X, Sadat S, Gehmert S, Alt E, Song YH. VEGF receptor Flk-1 plays an important role in c-kit expression in adipose tissue derived stem cells. *FEBS Lett* 2007; 581:4681-4684.
75. Wrage PC, Tran T, To K, Keefer EW, Ruhn KA, Hong J, *et al*. The neuro-glial properties of adipose-derived adult stromal (ADAS) cells are not regulated by Notch 1 and are not derived from neural crest lineage. *PLoS One* 2008; 3:e1453.
76. Aluigi MG, Coradeghini R, Guida C, Scanarotti C, Bassi AM, Falugi C, *et al.* Pre-adipocytes commitment to neurogenesis 1: preliminary localisation of cholinergic molecules. *Cell Biol Int* 2009; 33:594-601.
77. Georgiev DD, Taniura H, Kambe Y, Yoneda Y. Crosstalk between brain-derived neurotrophic factor and N-methyl-D-aspartate receptor signaling in neurons. *Biomed Rev* 2008; 19:17-27.
78. Lynch G. Glutamate-based therapeutic approaches: ampakines. *Curr Opin Pharmacol* 2006; 6: 82-88.
79. Lynch G, Rex CS, Chen LY, Gall CM. The substrate of memory: Defects, treatments, and enhancement. *Eur J Pharmacol* 2008; 585: 2-13.
80. Nagase T, Matsumoto D, Nagase M, *et al*. Neurospheres from human adipose tissue transplanted into cultured mouse embryos can contribute to craniofacial morphogenesis: a preliminary report. *J Craniofac Surg* 2007; 18:49-53.
81. Zhang Y, Nadeau M, Faucher F, *et al*. Progesterone metabolism in adipose cells. *Mol Cell Endocrinol* 2009; 298:76-83.
82. Cekic M, Sayeed I, Stein DG. Combination treatment with progesterone and vitamin D hormone may be more effective than monotherapy for nervous system injury and disease. *Front Neuroendocrinol* 2009; 30:158-172.
83. Sayeed I, Stein DG. Progesterone as a neuroprotective factor in traumatic and ischemic brain injury. *Prog Brain Res* 2009; 175:219-237.
84. Torres-Farfan C, Valenzuela FJ, Mondaca M, Valenzuela GJ, Krause B, Herrera EA, *et al*. Evidence of a role for melatonin in fetal sheep physiology: direct actions of melatonin on fetal cerebral artery, brown adipose tissue and adrenal gland. *J Physiol* 2008; 586:4017-4027.
85. Bartness TJ, Kay Song C, Shi H, Bowers RR, Foster MT. Brain-adipose tissue cross talk. *Proc Nutr Soc* 2005; 64:53-64.
86. Lee YH, Tharp WG, Maple RL, Nair S, Permana PA, Pratley RE. Amyloid precursor protein expression is upregulated in adipocytes in obesity. *Obesity (Silver Spring)* 2008; 16:1493-1500.
87. Lee YH, Martin JM, Maple RL, Tharp WG, Pratley RE. Plasma amyloid-beta peptide levels correlate with adipocyte amyloid precursor protein gene expression in obese individuals. *Neuroendocrinology* 2009; August 12: in print.
88. Ohta Y, Takenaga M, Tokura Y, Hamaguchi A, Matsumoto T, Kano K, *et al*. Mature adipocyte-derived cells, dedifferentiated fat cells (DFAT), promoted functional recovery from spinal cord injury-induced motor dysfunction in rats. *Cell Transplant* 2008;17:877-886.
89. Deng ZB, Poliakov A, Hardy RW, Clements R, Liu C, Liu Y, *et al*. Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance. *Diabetes* 2009; 12 August: in print.
90. Aoki N, Jin-no S, Nakagawa Y, Asai N, Arakawa E, Tamura N, *et al*. Identification and characterization of microvesicles secreted by 3T3-L1 adipocytes: redox- and hormone-dependent induction of milk fat globule-epidermal growth factor 8-associated microvesicles. *Endocrinology* 2007;148:3850-3862.