MINIREVIEW

Can obesity affect cognitive functions?

Jaroslav Pokorný, Jindřich Mourek

Institute of Physiology, First Faculty of Medicine, Charles University in Prague, Albertov 5, Prague, Czech Republic.

Correspondence to: Prof. Jaroslav Pokorný, MD., DSc., Institute of Physiology, First Faculty of Medicine, Charles University in Prague, Albertov 5, 128 00 Prague 2, Czech Republic. tel: +420224968416;
e-mail: jaroslav.pokorny@lf1.cuni.cz

Submitted: 2018-05-24 Accepted: 2018-05-28 Published online: 2018-06-30

Key words: **obesity; cognitive functions; metabolic hormones; cytokines; insulin hippocampus**

Act Nerv Super Rediviva 2018; **60**(1): 29–33 ANSR600118A01

Abstract

The association between nutritional status and cognitive function has its own history and has been studied from the philosophical, physiological and clinical points of view. Eating disorders, in addition to qualitative changes, can have two extremes – inadequate food intake with resulting malnutrition and conditions associated with excessive food intake and subsequent obesity. Obesity is a complex disorder associated with genetic disposition and factors of lifestyle. Obese people were found to have structural alterations of the specific brain systems, namely in the hippocampus. It can manifest in disturbances of long-term memory, attention, executive functions deficits (worse cognitive performance) and represents a risk factor for the development of dementia and Alzheimer disease. The endocrine role of adipose tissue, effects of metabolic hormones, cytokines, and fatty acids is discussed as well as epigenetic mechanisms that may modulate cognitive functions of the brain. Cognitive deficits induced by obesity are theoretically reversible. By elimination of those factors that lead to obesity, particularly by increase physical activity, exercise, walking, caloric restriction, the cognitive deficit can be reduced. Further discussion might deserve the generally accepted fact that most obese people have a positive assessment of their life. The relationship of obesity and cognitive function cannot be probably simplified in a relationship: slim thin = clever and stout fat = stupid (but happy?). On the other hand, it is almost futile to seek an overweight genius.

Introduction

The association between nutritional status and cognitive function has its own history and its justification. That history is linked to the teachings of Hippocrates and his four human fluids, that influence behavior and temperament of man. Such idea has not remained alone and in the form of Flechner's teaching (1801–1887) and the philosophy of psychophysical parallelism returned at the beginning of the 20th century in the form of categorization of humans into picnics and asthenias, with cyclothymic or schizothymic temperament.

Relation between the state and the quality of nutrition and the brain structure and function are studied and scientific investigated since time immemorial. Eating disorders, in addition to qualitative changes, can have two extremes – inadequate food intake with resulting malnutrition and conditions associated with excessive food intake and subsequent obesity. Starvation, along with other types of food deprivation and its effects on the developing brain and subsequent cognitive functions were discussed in the previous communication (Mourek at al 2010; Mourek & Pokorny 2016). Here we want to analyse the link between excessive food intake, activity of the adipose tissue and the

elementary and complex functions of neuronal circuits that have their parallels in the level of cognitive function and subsequent behavioural manifestations.

Reasons why to deal with the effects of excessive food intake result from the fact that in the northern hemisphere the number and percentage of population with higher overweight and obesity amounts to several tens of percent. Manifestation of obesity is called a pandemia and an idea was suggested that it is not only a complex socio-economic trend, but also a biological phenomenon which in affected individuals leads to the activation of immune, endocrine, and neuronal homeostatic systems, with the signs of stress reaction.

Mechanisms linking obesity and cognitive dysfunction

Obesity is a complex disorder associated with genetic disposition and factors of lifestyle. Obese people have significantly less brain tissue than people of normal weight (Raji *et al* 2010). Specifically, changes in the size of the hippocampus, the anterior cingulate gyrus, the frontal and temporal lobes and basal ganglia were described. At the same time, obesity is accompanied with disturbances of long-term memory, attention, executive functions deficits (worse cognitive performance) (Khan *et al* 2015; Kirton & Dotson 2016) and represents a risk factor for the development of dementia and Alzheimer disease (Jason *et al* 2014). Obesity in puberty, especially its central form, brings memory impairment and an earlier development of cognitive loss in old age (Bauer *et al* 2015).

Mechanisms that are responsible for the modulation of the structure and function of the brain by nutritional factors are multiple. With considerable simplification, we can categorize:

a. Mechanisms based on the control at cellular level, with visceral adipocytes playing the central role by producing a large number of information molecules that induce a state of non-specific inflammation. Cytokine released are responsible for vascular changes in the brain (associated with blood-brain barrier permeability alteration) and the activation of glial elements. Higher triglycerides and some fatty acids (unsaturated) might have similar effect (Miller & Spencer 2014; Enging 2017).
b. Activation of metabolic hormones (insulin, leptin, ghrelin, insulin-like growth factor-I, glucagon-like peptide-1 and others) modulates cell uptake of glucose (energy flows), and ultimately controls the expression of insulin and other receptors, and thus the capacity of specific neuronal circuits.
c. Direct effect of glucocorticoids, whose elevated levels are associated with the activation of defence mechanisms (stress reaction) that accompanies eating disorders, can lead to the loss of neurons, particularly in the hippocampus (Woolley *et al* 1990).
d. Epigenetic mechanisms involve relation of certain food components and signalling molecules released during the food intake and processing with the subsequent metabolic activation of the transcription of genetic information into functional proteins.

The role of cytokines and fatty acids

The shift in the evaluation of the relation between obesity and cellular regulations in the brain occurred a few years ago with the finding indicating that visceral adipocytes produce a large number of information molecules. Adipose tissue has been declared an endocrine organ (Hainer *et al* 2004; Haluzík *et al* 2004). This fact, however, also has its genesis: "ordinary" adipocyte, which until recently was mentioned in textbooks only in connection with energy reserve and thermoregulation, undergoes after the proliferation phase a complex differentiation process. This differentiation involves a number of steps, which are controlled by a variety of regulatory molecules. However, if the differentiation is modulated by proinflammatory cytokine (tumor necrosis factor alpha – TNF alpha) (there are two sensitive loci for this action), the process is defective and adipocytes become "non-physiological". These adipocytes (especially visceral fat) have then significantly larger volume with overproduction of proinflammatory cytokines (Hongyi *et al* 2013; Jason *et al* 2014; Pirola & Ferraz 2017).

In our report, only a few (specifically two) cytokines can be mentioned: Platelet Activating Factor (PAF) and Prostaglandin E-2 (PGE-2). Their production (together with other modulatory molecules) can be significantly potentiated. The oversized adipocytes can produce also Macrophage-Chemoatractive Protein (MCP), that attracts macrophages into the adipose tissue. Macrophages then can produce many other cytokines (including the proinflammatory ones) within the adipose tissue.

Another potentiation of this process represents the very activity of the above-mentioned PAF. Among others it activates phospholipase-A2 (PLA-2), which degrades phospholipids of the cell membrane (lipid bilayer) at the ester bond of the second position and releases arachidonic acid (AA). AA can immediately become a target of the enzyme cyclooxygenase, with consequent development of PGE-2. If AA undergoes lippoperoxidation process, leukotriene B4 (LTB4) is formed. It also exhibits a pronounced proinflammatory effects (Miller & Spencer 2014).

PAF belongs to the group of phospholipids (autacoids). It is recognised by NMDA receptors and it can significantly increase excitatory postsynaptic activity (long-term-potentiation). Resulting increase of intracellular calcium brings increased excitability, which manifests by increased number of spikes accompanied with the rise of excitatory neurotransmitter glutamate in the hippocampus (Wieraszko *et al* 1993). Activity of inhibitory processes (GABA) is not changed. The question arises whether such imbalance (between the

increased excitability and unchanged level of inhibitory processes) has functional manifestation in the complex neuronal circuit (e.g in the hippocampus). PGE2 has similar effects. Its presence significantly facilitates the transmission at the synapses; number of action potentials increases (without changing their amplitude). Similar results come from in in vitro experiments on isolated hippocampal pyramidal cell. Stimulation in the presence of PGE2 brings about higher frequency of action potentials (Chu & Bazan 2005; Tatsurou *et al* 2016). Adequate interpretation of those the findings is not simple. Prostaglandin molecule either alone or as the released arachidonic acid, can inhibit the Na^+-K^+ ATPase activity (Mourek 1988) and thus contribute to the depolarisation. Resulting "small depolarization" might constitute a basis for the elevated state of excitability. Another possibility (Yagami *et al* 2015) results from the increased production of PGE2 (both by neurons and glia cells), increased activity of PAK (protein kinase A) and through the cascade of cAMP the glutamatergic excitatory transmission is facilitated.

Another – and in our opinion a very serious explanations of the effects of information flows on the CNS obesity – is the fact that present Europeans (with few exceptions) suffer from a significant disproportion between the intake of Omega-6 and Omega-3 and always to the detriment of Omega-3. This deficit concerns mainly the long chain acid – Docosahexaenoic acid (DHA: 22: 6 n-3). The acid represents up to 20% portion in the membranes of nerve elements. This imbalance, reaching values of 15:1 (!) can lead to changes in the function of synaptic membranes: Aging, which is accompanied with the loss of DHA in the lipid bilayer, leads to a significant decrease of a response to a standard stimulus. Administration of DHA in the diet can restore the situation and return the response back to "normal" (McGahon *et al* 1999). Disturbances in the composition of neuronal membranes (i.e. proportions and relations between different groups or even individual fatty acids as well as the representation of individual phospholipid heads and their location in the membrane) bring about alteration of the optimal niche (environment) for "implantation" functional proteins. Specific and therefore physiological (optimal) set of individual components of the membrane thus constitutes condition "sine qua non" for the functional capacity of membrane proteins.

We suggested three factors (PAF, PG2 and imbalance between unsaturated fatty acids with the long chain – omega-6 and omega-3) that in different extent could affect synaptic excitability. So far it certainly applies to the pyramidal cells of the hippocampus.

It can be therefore hypothesized that obesity becomes a modulator of its own neural activity. Additionally, we remember that both proinflammatory cytokines as well as DHA can affect gene expression. In the case of DHA, it is known that it inhibits production of proinflammatory cytokines (TNF-alpha, IL-6, IL I) (reviewed Mourek *et al* 2007; Das 2004).

It is logical that the data presented here have still many vacant spots. The first and fundamental question is whether the described changes in excitability have for the obese people any „biological significance". They can of course represent a non-physiological state. We do not know whether the described phenomena can be induced in all structures and circuits of the brain or whether it is only a selective factor (in terms of space but also the time) (Shefer *et al* 2013).

The role of metabolic hormones

Obesity, insulin-resistant form of diabetes and metabolic syndrome have common characteristics and also have specific shared pathogenetic mechanisms. Some obese people develop insulin-resistant form of diabetes, and even in the absence of metabolic and cardiovascular co-morbidity the risk of dementia and Alzheimer's disease is in obese higher (Rotterdam study Ott *et al* 1996). Alzheimer's disease is therefore sometimes referred to as " type III. diabetes ". The association between obesity and diabetes brought the concept of Diabesity (Sims *et al* 1973).

Metabolic hormones (insulin-like peptides) exhibit effects of growth factors. They can be formed at the place of action (paracrine action) or they are released into the blood stream and transmitted even across the blood brain barrier. Besides peripheral growth effects (e.g. angiogenesis) they can affect neurogenesis, differentiation and neuronal death, angiogenesis in the brain, modulation of neurotransmitter release and modulation of receptors sensitivity. This way, neuropeptides control the function of neuronal circuits (relations between excitation and inhibition, formation and retrieval of memory traces) and also the complex brain functions such as cognitive processes or food intake (Bennet at al 1997).

The role of insulin in the development of cognitive disorders

mRNA for synthesis of insulin has been demonstrated in many areas of the brain (olfactory area, amygdala, hippocampus, pyriform cortex, thalamus) (Michael *et al* 1992). Furthermore, insulin from peripheral sources is transmitted across the blood brain barrier proportionally to its plasma level.

Insulin receptors can be found in neurons and glial cells and they are notably expressed in areas related to cognition (hippocampus, frontal cortex). They are present at the synapses, especially in their postsynaptic element (Schulingkamp *et al* 2000; Wang *et al* 2015).

Chronic hyperinsulinemia and insulin resistance decrease the expression of insulin receptors (down-regulation) and induce insulin deficiency in the brain. Insulin resistance is considered as one of the pathogenetic mechanisms of dementia in Alzheimer's disease (AD is called 'diabetes type III.") (de la Monte 2009).

Experimental high caloric diet in rats, brings memory impairment and structural changes in the hip-

pocampus and frontotemporal cortex. High-fat diet in rats causes disturbances of insulin signalling and mitochondrial homeostasis.

Classical pathway of action of insulin leads through binding to insulin receptor, to the activation of the phosphatidylinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) and to increased glucose transport into cells (e.g. adipocytes). In the brain, this mechanism contributes only very little to glucose uptake, because transport of glucose does not require presence of insulin.

So called "Non-canonical" action of insulin involves activation of protein kinase-C, which affects trophic functions, i.e. survival and neuronal death by means of expression inhibition of pro-apoptotic factors. Insulin also acts on expression and recycling of AMPA and NMDA receptors, and thus enters into the control mechanisms of neuroplasticity (the growth of dendrites and axons, synapses formation and elimination. (Verdile *et al* 2015; Stranahan 2015).

The role of leptin

Obesity can be associated also with leptin resistance. Leptin is released primarily from adipocyte, its plasma levels are proportional to the amount of adipose tissue in the body and it has an anorexigenic effect. Leptin is transported into the brain through the blood-brain barrier in an amount proportional to its plasma concentration. Leptin receptors are expressed in most regions of the CNS, particularly high density they reach in hippocampus.

In the experiment, leptin enhances NMDA efficiency of synaptic transmission by induction of the long-term potenciation (LTP) at synapses of the CA1 hippocampal region. Leptin also promotes the growth of dendrites and synapses (neuroplastic action). Mice with defective leptin signalling, therefore have a lower density of synapses in the hippocampus, which is combined with spatial memory disorders (Farr *et al* 2006; McGregor *et al* 2015).

Epigenetic regulation

Some components of food can interfere with the expression of genetic information without getting involved with DNA sequences. Similar effects have also some wide-ranging factors such as the long-term shortage of food, especially in the period of development (Mourek & Pokorny 2016), intense physical activity, stress, etc.

In the processes of DNA methylation, or nuclear histones modification, can be directly influenced by many substances present in the food (folate, vitamin B6 and B12, choline, methionine).

Reversibility of cognitive deficits induced by obesity (treatment and prevention)

Means of enhancing cognitive functions are generally very inefficient. Significant therapeutic and preventive effect should be therefore elimination of those factors that lead to obesity, particularly to increase physical activity, exercise, walking, caloric restriction, which increase sensitivity to insulin. It is also the way haw to reduce the developing cognitive deficit. In the experiment such simple interventions were effective (Davis *et al* 2011; Ho *et al* 2011).

Pharmacotherapeutic modification of inflammatory cytokines levels and activation of anti-inflammatory cytokines could be the treatment for extreme cases (Khorassani *et al* 2015; Mazur-Biały *et al* 2017).

Beneficial appears administration of anti-diabetic drugs (e.g., metformin) for the reduction in insulin resistance. Similar effects can have also and GLP-1 mimetic substances (e.g. Liraglutide). These substances can cross the blood-brain barrier and have neuroprotective effects together with positive effect on cognitive function. Also intranasal insulin administration in AD patients with mild memory disorders, and in patients with moderate cognitive deficiencies had positive effect (Kullmann *et al* 2017; Chen *et al* 2017; Kakkar & Dahiya 2015). In experiments, beside insulin, also leptin, Vascular endothelial growth factor (VEGF), and Brain-derived neurotrophic factor (BDNF) had promising effect.

Conclusions

Even very fine alteration of cognitive function accompanying obesity, may bring changes in behavior, especially in the spectrum of executive functions. This could explain the preference for obesogenic food in already obese and a thus further deterioration in their state (*circulus viciosus*).

However, further discussion might deserve the generally accepted fact that most obese people have a positive assessment of their life. The relationship of obesity and cognitive function cannot be probably simplified in a relationship: slim thin = clever and stout fat = stupid (but happy?). On the other hand, it is almost futile to seek an overweight genius.

Acknowledgement

Supported by the grant PROGRES Q35/LF 1.

REFERENCES

1 Bauer CCC, Moreno B, González-Santos , Concha L, Barquera S, Barrios FA (2015). Child overweight and obesity are associated with reduced executive cognitive performance and brain alterations: a magnetic resonance imaging study in Mexican children. *Pediatr Obes*. **10**(3): 196–204.

2 Bennett GW, Ballard TM, Watson CD, Fone KCF (1997). Effect of neuropeptides on cognitive function. *Exp Gerontol*. **32**(4–5): 451–469.

3 Chen Y, Dai CL, Wu Z, Iqbal K, Liu F, Zhang B, Gong CX (2017). Intranasal insulin prevents anesthesia-induced cognitive impairment and chronic neurobehavioral changes. *Front Aging Neurosci*. **9**: 136.

4 Chu Ch & Bazan N (2003). Endogenous PGE2 regulates membrane excitability and synaptic transmission in hippocampal CA1 pyramidal neurons. *J Neurophysiol*. **93**: 929–941.
5 Das UN (2004). Perinatal supplementation of long-chain polyunsaturated fatty acids, immune response and adult diseases. *Med Sci Monit*. **10**(5): HY19–25.
6 Davis CL, Tomporowski L, McDowell PD, Austin JE, Miller BP, Yanasak PH, *et al* (2011). Exercise improves executive function and achievement and alters brain activation in overweight children: A randomized, controlled trial. *Health Psychol*. **30**(1): 91–98.
7 De la Monte SM (2009). Insulin resistance and Alzheimer's disease. *BMB Rep*. **42**(8): 475–481.
8 Enging A (2017). The pathogenesis of obesity- associated adipose tissue inflammation. *Adv Exp Med Biol*. **960**: 221–245.
9 Farr SA, Banks WA, Morley JE (2006). Effects of leptin on memory processing. *Peptides*. **27**(6): 1420–1425.
10 Hainer V, Finer N, Tsigos C, Basdevant A, Carruba M, *et al* (2004). Management of obesity in adults: project for European primary care. *Int J Obes*. **28**: S226–S231.
11 Haluzík M, Pařízková J, Haluzík MM (2004). Adiponectin and its role in the obesity-induced insulin resistance and related complications. *Physiol Res*. **53**: 123–129.
12 Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, *et al* (2011). The effects of physical activity, education, and body mass index on the aging brain. *Hum Brain Mapp*. **32**: 1371–1382.
13 Hongyi Li, Xiao Ch, Lizeng G, Qien Qi, Gang S, Qingyan J, *et al* (2013). MiRNA-181a regulates adipogenesis by targeting tumor necrosis factor-α (TNF-α) in the porcine model. *PLoS One*. **8**(10): e71568, doi: 10.1371/journal.pone.0071568.
14 Jason CD, Nguyen A, Killcross S, Jenkins TA (2014). Obesity and cognitive decline: role of inflammation and vascular changes. *Front Neurosci*. **8**: 375, doi: 10.3389/fnins.2014.00375.
15 Kakkar AK & Dahiya N (2015). Drug treatment of obesity: Current status and future prospects. *Eur J Intern Med*. **26**(2): 89–94.
16 Khan NA, Baym CL, Monti JM, Raine LB, Drollette ES, Scudder MR, Moore RD, Kramer AF, Hillman CH, Cohen NJ. (2015). Central adiposity is negatively associated with hippocampal-dependent relational memory among overweight and obese children. *The Journal of Pediatrics*. **166**(2): 302–8.
17 Khorassani FE, Misher A, Garris S (2015). Past and present of anti-obesity agents: Focus on monoamine modulators. *Am J Health Syst Pharm*. **72**(9): 697–706.
18 Kirton JW & Dotson VM (2016). The interactive effect of age, education, and BMI on cognitive functioning. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. **23**(2): 253–262.
19 Kullmann S, Heni M, Veit R, Scheffler K, Machann J, Haring HU, *et al* (2017). Intranasal insulin enhances brain functional connectivity mediating the relationship between adiposity and subjective feeling of hunger. *Sci Rep*. **7**(1): 1627.
20 Mazur-Biały A, Bilski J, Pochec E, Brzozowski T (2017). New insight into the direct anti-inflammatory activity of mayokine irisin against proinflammatory activation of adipocytes. Implication for exercise in obesity. *J Physiol Pharmacol*. **68**(2): 243–251.
21 McGahon BM, Martin DS, Horrobin DF, Lynch MA, (1999). Age-related changes in synaptic function: analysis of the effect of dietary supplementation with ω-3 fatty acids. *Neuroscience*, **94**(1): 305–14.
22 McGregor G, Malekizadeh Y, Harvey J (2015). Food for thought: regulation of synaptic function by metabolic hormones. *Mol Endocrinol*. **29**(1): 3–13.
23 Michael W, Schwartz D, Figlewicz DG, Baskin Stephen C, Woods DP Jr (1992). Insulin in the brain: a hormonal regulator of energy balance. *Endocr Rev*. **13**(3): 387–414.
24 Miller AA & Spencer SJ (2014). Obesity and neuroinflammation: a pathway to cognitive impairment. *Brain Behav Immun*. **42**: 10–21.
25 Mourek J (1988). Arachidonic acid-induced inhibition of (Na^+ K^+)-stimulated ATPase in the cerebral cortex and medulla oblongata of young and adult rats. *Physiol Bohemoslov*. **37**(5): 427–31.
26 Mourek J, Zvolský P, Pokorný J (2010). Formative processes of CNS maturation – The genesis of neuropsychiatric disorders and the strategy of optimal development. *Act Nerv Super Rediviva*. **52**(3): 127–132.
27 Mourek J & Pokorný J (2016). Mechanismy adaptace CNS na působení postnatální zátěže. *Čes a slov Psychiat*. **112**(1): 44–48.
28 Mourek J a kol. (2007). Mastné kyseliny Omega-3: zdraví a vývoj. Praha: Triton, ISBN 8072549177.
29 Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM (1996). Association of diabetes mellitus and dementia: The Rotterdam Study. *Diabetologia*. **39**(11): 1392–1397.
30 Pirola L & Ferraz JC (2017). Role of pro- ad anti-inflammatory phenomena in the physiopathology of type 2 diabetes and obesity. *World Biol Chem*. **8**(2): 120–128.
31 Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, *et al* (2010). Brain structure and obesity. *Hum Brain Mapp*. **31**(3): 353–364.
32 Schulingkamp RJ, Pagano TC, Hung D, Raffa RB (2000). Insulin receptors and insulin action in the brain: review and clinical implications. *Neurosci Biobehav Rev*. **24**(8): 855–872.
33 Shefer G, Marcus Y, Stern N (2013). Is obesity a brain disease? *Neurosci Biobehav Rev*. **37**(10): 2489–2503.
34 Sims EA, Danforth E Jr, Horton ES, Bray GA, Glennon JA, Salans LB (1973). Endocrine and metabolic effects of experimental obesity in man. *Recent Prog Horm Res*. **29**: 457–496.
35 Stranahan AM (2015). Models and mechanisms of hippocampal dysfunction in obesity and diabetes. *Neuroscience*. **309**: 125–139.
36 Verdile G, Fuller SJ, Martins RN (2015). The role of type 2 diabetes in neurodegeneration. *Neurobiol Dis*. **84**: 22–38.
37 Wang J, Freire D, Knable L, Zhao W, Gong B, Mazzola P (2015). Childhood and adolescent obesity and long-term cognitive consequences during aging. *J Comp Neurol*. **523**(5): 757–768.
38 Wieraszko A, Gang L, Kornecki EV, Hogan MV, Ehrlich YH (1993). Long-term potentiation in the hippocampus induced by platelet-activating factor. *Neuron*. **10**(3): 553–557.
39 Woolley CS, Gould E, McEwen BS (1990). Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal neurons. *Brain Res*. **531**(1–2): 225–231.
40 Yagami T, Koma H, Yamamoto Y. (2016). Pathophysiological roles of cyclooxygenases and prostaglandins in the central nervous system. *Molecular neurobiology*. **53**(7): 4754–71.