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MINIREVIEW

Polyphenols and cognitive pathophysiology: Potential relationships to health and lifestyle?

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Abstract

This short review reacts to publications pointing to several suggested lifestyle modifications activating nitric oxide synthases. As a result the positive changes in cardiovascular system and brain circulation with subsequent cognitive impairment were described. Among such modifications the nutritional habits and physical activities are recommended during early pathophysiological/reversible stages primarily. Nowadays, quite a lot of nutritional supplements, even as the bonuses for several specialized programs of physical activities are at disposal. Among them, the polyphenols may be mentioned as frequently discussed in basic scientific as well as prospective clinical studies. They are commended as regulatory promoters of interrelations among oxidative stress, lifestyle, nutrition and cognition. We would like to remark that even the utilization of physical activities and nutrition may trigger the central regulatory brain mechanisms earlier than the peripheral, especially, blood flow ones. Moreover, they can have the positive effect upon the aging of human cognitive functions as well. The use of the standard human psychophysiological methods can reveal valid indicators of such effects. As an example the electrophysiological markers of sensorimotor integration are illustrated. This integration serves the interindividual communication as well as between men and his/her environment. Changes in visual-oculomotor integration reflecting the impact on the intentionally and reflexively triggered central regulations and also the increase of the overall brain cortex activity will be mentioned even after single use of polyphenols. Such an approach may offer more informative correlates of changed individual lifestyle as well as to follow the long-term impact on the healthy physical and cognitive aging.

Lifestyle and oxidative stress

In essence, the lifestyle is a social factor containing also a dimension of value orientation. As an important factor the mental pre-set of the individual has to be taken into the consideration as playing a dominant role in effort to modify his/her behaviour (lifestyle change). The physical activity and some aspects of nutrition, as important parts of the individual´s lifestyle, may influence the production of free reactive oxygen species (ROS) and the body ability to counteract or detoxify their harmful effects upon the health. The imbalance in the above mechanism results in the oxidative stress. The role of the nitric oxide (NO) in regulation the balance between ROS and the antioxidant mechanisms is well documented as multifaceted and important for both normal function and pathophysiological response (Loscalzo & Welch 1995). As the health and ill-health are bio-psycho-socially determined the interplay of lifestyle, physical activity, nutrition and the role of the NO balance as consequence of this also gained the important accent. Contrarily to the longer history of the role of NO in cardiovascular disorders already in 2008 there were published papers pointing out the role NO in prevention of cognitive disorders. The experimental data have confirmed that down-regulation of inducible nitric oxide synthase (iNOS) and up-regulation of endothelial NOS (eNOS) play important role in protecting against disorders of cognitive functions (Cai *et al* 2008; Manikhina *et al* 2008).

It is known that the oxidative stress leads to harmful oxidation of lipids, proteins and nucleic acids as well as to changes in gene expression. The animal experiments have shown that several transcription factors in response to oxidative stresses could be important for aging by suppressing the accumulation of oxidative stresses and deoxyribonucleic acid (DNA) damage (Dongping & Yang 2011; Canning *et al* 2015). The last decade was very rich also in offering data on the role of genetic variability of several genes in behaviour and brain activity of subjects. If the products of oxidative stress are not immediately deactivated or removed by antioxidant pathways, they might accumulate in cells (Terman & Brunk 2006) and damage lipids, proteins and DNA (Popa-Wagner *et al* 2013). To diminish these effects, the NO, among others, may play a relevant role since its properties are ideally suited for its role as a transcellular messenger (Garthwaite 2008). Moreover, it utilizes multiple signalling pathways and their combinations to control activity of genes.

According to the generally accepted proposal, increased ROS generation with subsequent decreased NO bioavailability is the most important cause of impaired endothelium-dependent relaxation in different cardiovascular diseases (Schulz *et al* 2008) which favour the beneficial effect of antioxidant treatment in such diseases. Many experimental studies are in accordance with this proposal. The NO may be assumed to play one of the important roles in preservation the functional integrity of the neurovascular unit. This should be related in further studies with different diseases (Farah *et al* 2018; Steinert *et al* 2010).

However, clinical studies on chronic antioxidant therapy with classical vitamins like A, C, E fail to confirm the beneficial effect in cardiovascular diseases (for review see Pechanova & Simko 2009). Also in the well-known Heart Outcomes Prevention Evaluation (HOPE) study, involving patients with atherosclerotic complications of diabetes mellitus, vitamin E in the dose of 400 IU daily was not able to reduce blood pressure and morbidity and mortality from cardiovascular reasons (Yusuf *et al* 2000). It should be also pointed out that giving large doses of dietary antioxidant supplements to human subjects has demonstrated little or no preventative effects in most studies (Halliwell 2013). Several factors have been suggested as potential causes participating in the failure of antioxidant treatment, such as the type of antioxidant used, its dose, duration of treatment, pro-oxidant properties and different compartmentalization of a particular antioxidant dosage and generated ROS. Using antioxidant with additional value, e.g. ability to decrease ROS along with increasing endothelial nitric oxide synthase (eNOS) expression/activity, may have a greater chance to succeed in the treatment of cardiovascular, but also metabolic or mental disorders. Different polyphenol compounds have been already shown to have such effect (Galleano *et al* 2010; Jagla & Pechanova 2015).

Influence of physical activities

Nowadays, our time is characterized by reduction of physical activity and increased demands on mental activities with a parallel increase of stressful situations. One consequence is the sedentary style of everyday living and frequently together with unhealthy nutrition in the sense of the so-called fast foods. Such behaviour is one of the most responsible factors for the contemporary epidemics of obesity and associated metabolic abnormalities. The reduction in physical activity together with not very healthy dietary habits triggers profound alterations in the gut and interrelated visceral fat. As the result the altered gut micro biota composition and impaired gut barrier function originate. An increased release of bacteria-derived factors such as endotoxins and proinflammatory cytokines takes place. No wonder that Konrad and Weest (2014) discussed the so-called gut-liver axis which may have the hard consequences for the cardiovascular (patho) physiology. Moreover, the gut and brain may influence each other through variety of pathways, including the enteric autonomous nervous system, nervus vagus, immune system or metabolic processes of gut microorganisms. Thus, the nutrition has also impact on the so-called gut-brain axis (Mayer *et al* 2015; Zhu *et al* 2017). These authors pointed out the relationship between gut micro biota and various brain disorders and disease.

Not so frequently and even more seldom, the participation and role of higher brain regulatory mechanisms are taken into account in spite of the fact that the physiological effects of nutrient components affect also the brain biochemistry. Consequently, in such a way they may enter the brain functions regulation. In other words, *nutrients may give how to function*. Physical activities and/or exercises make up a significant part of our everyday behaviour. The recent data demonstrate the important role of physical training and NO in improving health of subjects suffering from cardiovascular and degenerative diseases. The relevant literature points to the protective mechanisms of physical exercise linked to increase of endothelial synthesis of NO as well as of vascular endothelial growth factor (Dyakova *et al* 2015; Umegaki 2015; Alvim Agricola *et al* 2017).

As for the relation among physical activity and the above mentioned issues, Elosua *et al.* (2003) pointed out that even a short exercise session may be enough to activate antioxidant mechanisms. Hypertension, dyslipidaemia, uncontrolled diabetes, hyperinsulinemia, metabolic syndrome and high levels of inflammatory markers were shown to be modifiable by the changes in exercise levels In general; fitness training is useful to increase energy expenditure and thereby to contribute to the positive energy balance. It could also to attenuate the activation of several signalling pathways of inflammation and oxidative stress (Krűger *et al* 2016).

Since 90-ties last century it is known that that physical fitness and basal NO production are positively linked to each other. The higher NO production at rest was observed in well-trained subjects due to their regular physical activity (Jurgersten *et al* 1997). Moreover, NO production increases during exercise and may be involved in the increases in exercise-induced glucose transport and skeletal muscle blood flow and force production, all of which suggest that NO is a key mediator of exercise metabolism (Balon & Nadler 1997; Roberts *et al* 1999). As Brown *et al.* (2013) concluded the evidence for physical activity being a contributor to healthy brain aging is strong. They reviewed studies in this area which confirmed that physical activity can help maintain superior cognitive functioning as well as modify the risk of cognitive decline, Alzheimer disease and dementia.

Multiple sources of NO exist in skeletal muscle, including the vascular endothelium which expresses eNOS and the skeletal myocytes which express nNOS. Interestingly, nNOS content in human skeletal muscle is 60% higher in athletes than non-athletes, while studies investigating eNOS have provided conflicting results. Inducible NOS is only expressed in skeletal muscle during inflammatory responses (for review see Zembroń-Łacny *et al* 2013). In healthy muscle, NO derived from nNOS has been implicated in myofiber differentiation, modulation of contractile force, and exercise-induced glucose uptake. Recent in vivo experiments suggest that skeletal muscle-derived NO also plays an important role in the regulation of blood flow in exercising skeletal muscle by modulating the vasoconstrictor response to activation of α-adrenergic receptors (for review see Magrone *et al* 2017).

On the other hand, results of Tomiga *et al.* (2017) suggest that high fed diet (HFD)-induced brain dysfunction may be caused partially by increase in hippocampal and/or cortical nNOS, and that exercise may have therapeutic potential for the treatment of HFD-induced depression and anxiety via the decrease in nNOS/NO level. It could be hypothesized, that nNOS overexpression and NO overproduction impair neuronal function and lead to neurodegeneration similarly like it is in iNOS expression. Exercise may reduce this process. Similarly, different polyphenolic compounds including that in green tea may reduce ROS/NO overproduction and consequent apoptotic process (Guo *et al* 2005). Also results of Shi *et al.* (2003) suggest that tea polyphenols significantly inhibits apoptosis of the tubular and interstitial cells in rats with cyclosporine-induced chronic nephrotoxicity.

The supposed relationship between physical activity and higher brain functions began to be studied 50 ago. Now, it is generally accepted that the physical activity improves both physical and mental fitness. Gajewski and Falkenstein (2016) concluded that the higher-level human brain functions such as executive functions are more improved by physical training than lower-level functions. It has to be certainly accepted because the modern fitness activities demand the more complex sensorimotor integration having in mind the visual, tactile and vestibular control as well as the brain preparation to program not only to move but to form the succession of the rather complex motor activities under the personal intentional control. It can be taken as a support of their conclusion that *combined programs which embrace both aerobic, force and coordination training are more favourable since the different aspects of such training induce different brain and behavioural changes*. The authors also suggest that in future studies of this relation to use non-invasive neurophysiological methods such as e.g. electroencephalography will be important. The same is our point of view that for analysing the results of the programs for individual behaviour modification also the behavioural and biomedical risk factors, personality traits factors, mental ill health factors, family-related, social, genetic, demographic and environmental factors have to be individually assessed – not only at least but as much as possible.

Influence of nutrition

As stated above, the oxidative stress results in alteration of lipids, proteins and nucleic acids and is considered to play an important role in the pathogenesis of aging also. The human body has developed several endogenous anti-oxidative stress protective mechanisms (Masella *et al* 2005). The other mechanisms, exogenous, can be triggered and supplied by means of the diet as well. The effects of polyphenol compounds have been widely studied for their strong antioxidant properties. Taking away the question what is more important for health and healthy aging – the polyphenols or their metabolites, one has to agree with Sies (2010) that more important question is their bioavailability versus their antioxidative properties. Another important question was discussed by Vazour *et al.* (2017). In their recent very important and seminal paper concerning the nutrition for aging brain the authors pointed out that the precision and accuracy of dietary intake estimation is difficult and because of this the associations observed between polyphenols and health are compromised. Moreover, according these authors it is still challenging to develop personalized diet-recommendations for dietary polyphenol intake. We are sure that the personalized diet-recommendations are not easy to introduce in general practice. Further research is needed to evaluate the potential effects of natural antioxidants supplements in antioxidant-based therapy (Liu *et al* 2018). The latest published results are encouraging in the supplementary therapy of involutionary changes in some of the cognitive functions by natural polyphenols (Bensalem *et al* 2019). On the other hand, a personalized estimation of the effect of say polyphenols upon the selected cognitive functions could be done by using the non-invasive psychophysiological measurements which we suggest by this contribution.

It was shown that the oral administration of polyphenols in rats reduced the oxidative stress (Pechanova 2010), inhibited ROS generation in their brains, activated the neuronal NO synthase, down regulated the proinflammatory transcriptional factors such as nuclear factor kappa B (NF-κB) and modulated the signalling pathways such as mitogen-activated protein kinase cascade and cyclic adenosine monophosphate (cAMP) response element-binding protein (Magrone *et al* 2017; Parohova *et al* 2009; Kovacsova *et al* 2010). Such effects can lead to the improvement of memory and cognitive performances well.

The effect of administration of polyphenols in healthy subjects upon the human higher brain functions could be mediated via various higher brain regulatory mechanisms (Joris *et al* 2018).

Therefore, also the registration of changes in sensory-motor integration, mainly in visual-oculomotor integration which are the most tight and precise kind of the sensorimotor integration in humans, may offer reliable data. The use of the electrooculography (EOG) and electroencephalography (EEG) as a correlates of the sensorimotor integration allow to study closer this question. Recent experiments in our laboratory have shown that NO is involved also in sensorimotor gating and may add to the knowledge of pathogenic mechanism of mental disorders (Rovný *et al* 2018).

Analysis of sensorimotor integration

The analysis of the accuracy of several thousands of visually triggered saccadic eye movements (SEMs), bringing the visual target onto the retinal fovea, in several hundreds healthy volunteers repeatedly approved that 95% of visually-guided SEMs are accurate when moving the eyes for 100 to fixate the new fixation target. The inaccuracy did not exceed 0.5° (Jagla *et al* 1992). The oral administration of a single dose of the polyphenol substance increased the number of accurate visually-guided SEMs to 98% ($p<0.02$) and the angular dimension of their inaccuracy was significantly diminished. The programming of the SEMs in the brain was shorter, but the time of the first encoding the basic characteristics of the visual stimuli in the cerebral cortex was not affected (Jagla 2016).

The SEMs elicited by memory information means no reflex but intentional movements generated by subjective decision. The memory guided SEMs are, in general, more inaccurate in comparison with visually evoked ones (30%: 5%, $p<0,001$). The value of memory guided SEMs inaccuracy is significantly higher than with visually triggered reflex saccades (1.2–1.5°: 0.5°, $p<0.001$). The number of inaccurate SEMs decreases significantly after polyphenols administration (18%: 30%, $p<0.01$) but it is still significantly higher than following the reflex saccades. At the same time the value of their inaccuracy significantly decreased (0.7°: 1.2–1.5°, $p<0.02$) and was similar to the value with visually evoked SEMs. During the preparatory period for saccades guided by memory information the significant decrease of the slow EEG bands, alpha power mainly, was registered. The recordings have shown this decrease over the broad temporo-parietal cortex bilaterally (Cimrová *et al* 2011).

Such movements are the result of the co-operation between the frontal and parietal cortical areas via the cortico-cortical and cortico-subcortico-cortical neuronal connections. Many of these connections form rather largely segregated circuits dedicated to specific aspects of sensory-motor transformation. These „independent modules" can be considered as the functional units of the cortical motor system (Luppino & Rizzolatti 2000). The fronto-parietal connections play a significant role in cognitive functions as well. Hauert (1986) has formulated the hypothesis that the motor function is a cognitive function. Between setting the purpose of movement and its actual execution, integration between motivational, perceptual, and previously overlearned motor components take place.

Conclusion and how to proceed?

The importance of the fronto-parietal connections in relation to the memory guided SEMs generation was documented (Pierrot-Desseiligny *et al* 1991). The frontal part is important mainly as an executive manager. The tied up temporal connections via parietal part of circuitry are involved in space orientation, grasping in space and memory functions. With memory guided SEMs the subject is in situation of divided attention, a part of his/her attention is focussed on the generation the eye movements and the other one upon the accurate landing the eyes on the desired location. The question is whether the polyphenols affected more spatial memory or attention. We are of opinion that it is a higher activation of spatial memory functions probably because the value of memory guided SEMs inaccuracy after the polyphenols administration approached the one of visually guided SEMs. Nevertheless, we are aware also that the more sophisticated measurements are needed.

Experimental research has shown that polyphenols and their metabolites are found at lower concentrations in the brain than other antioxidants. Therefore, it is unlikely that antioxidant actions of polyphenols alone can account for cognitive effects. It has been suggested that polyphenol effects on the brain are mediated by protection of neurons, enhancement of neuronal function and their growth. Polyphenols may exert neuroprotective actions via interaction with specific proteins which are the most important part of intracellular signalling cascades crucial for neuronal survival (Spencer 2008). Moreover, they have the potential to induce new protein synthesis in neurons and could have a direct effect on cognitive performance, particularly memory (Williams *et al* 2008; Giacalone *et al* 2001). The improvements in vascular function and increased blood flow in the brain may also contribute to cognitive benefits. The results of the functional magnetic resonance imaging (fMRI) studies point to correlations between cerebral blood flow and cognitive function in humans (Spencer 2010). On the other hand, the results have shown that polyphenols elicited the activation of the cortex (Ruitenberg *et al* 2005; Cimrová *et al* 2011). This can also be taken as an important mechanism supporting the better cognitive functioning. In this short review we tried to illustrate that not only the oxidative stress, lifestyle, nutrition and cognition, but also the factors influencing them are very rich and mutually interrelated.

The concept of the brain executive functioning implies processes that control the other brain processes. Our executive functioning evolves – in line – with modifications in our lifestyle as well. The executive functions of our brain control also the hierarchically lower brain functions. They can be studied on the level of the sensorimotor functions. And the most tight and precise sensorimotor integration is the visual-oculomotor one. In this humble contribution, we attempted to outline some considerations aroused from our previous animal and human studies. The above example of the effects of single dose of polyphenols illustrates how the administration of a biological active natural substance, even a single one, can affect the brain cortex activity more rapidly in comparison to the peripheral effects (e.g. body organs, vessels etc.) precisely described by *in vitro* and animal experiments. Analysis of appropriate sensorimotor function allows study selected cognitive function and its changes, namely. Sometimes, this may be more important than the *in vitro* and animal studies point to. Such an approach may help, in future, to take into account possible participations of mechanisms that are domains of neurobiology of behaviour, integrative physiology and psychosomatic relations, e.g. mental set, attention to inner and outer activities as also personal characteristics. It must be kept in mind that the mental set of a given person can affect the interrelation of age, nutrition, every day´s activities as also the effects of pharmacotherapy. Altogether, it suggests for using the methods of the non-invasive psychophysiology together with particular psychological personality traits assessments as well in addition to basic and needed biological approaches.

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Availability of data and materials

The data and experimental procedures of authors are described in detail in their publications provided in References.

Conflict of interests

The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interests.

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