Cognitive training in neurodegenerative diseases: a way to boost neuroprotective molecules?

Neurotrophins, and growth factors in general, are proteins which exert many actions in central nervous system neurons. Neurotrophins promote the survival and neuronal function of neurons and exert neuroprotective effects in pathological models of neurodegenerative diseases. In humans several clinical trials based on the use of these proteins have been carried out. Among them, it is worth to mention gene therapy especially in Parkinson's disease (PD) (Kordower and Bjorklund, 2013), and a series of experiments using vectors capable of carrying neurotrophins in the selected target region where they can exert their beneficial action (Ghosh et al., 2014).

A common denominator of these therapeutic approaches is the attempt to restore, or at least limit, the damage of neuronal function by increasing neurotrophins availability. In this regard, we have recently proposed a cognitive rehabilitation protocol in PD patients, in which we used as a possible biomarker of the effects of cognitive training the serum levels of the neurotrophin brain-derived neurotrophic factor (BDNF) (Angelucci et al., 2015), a specific trophic factor for dopaminergic neurons. We found that the cognitive rehabilitation had beneficial effects on cognitive deficits of these patients in association with an increase in BDNF serum levels.

What are the implications of these findings? First of all, we are describing an endogenous effect and not an effect of a drug treatment. This means that the increased availability of BDNF may represent a response to the stimulation produced by the cognitive treatment. Numerous studies have shown that PD patients have reduced peripheral and central levels of BDNF and that drugs able to improve the motor symptoms also elevate these levels. Thus our findings suggest that the combination of drug treatment and cognitive training may have beneficial effects in PD patients with a mechanism which includes the stimulation of BDNF production.

Nonetheless, many other things still need to be clarified. We have observed an improvement in cognitive function and an increase in BDNF serum levels. Whether these changes are permanent or not, it is still a matter of investigation. Moreover, we still do not know if this increase in BDNF is beneficial to the damaged neurons. Nevertheless, it is encouraging the fact that in animal models, BDNF infusions directly into the basal ganglia (nucleus accumbens) was able to restore cognition, synaptic plasticity, and cell signaling in cognitive impaired aged rats (Li et al., 2012). Moreover, these effects in animal models are also present in other neuropathological conditions such as stroke, Alzheimer's and Huntington's diseases, depression and spinal cord injury. In human subjects, it has been shown that BDNF increases after physical exercise (Vaughan et al., 2014), and this increase may correlate to improvement of cognitive functions in pathological conditions such as stroke and depression. Moreover, other studies have shown that serum BDNF levels in PD patients might change in relation to other types of rehabilitations such as intensive motor training and these effects are associated with motor improvements.

Another issue may be the fact that serum BDNF level may not reflect the BDNF level in the brain. However, a correlation between central and peripheral BDNF levels has been suggested in animal models and humans. It was demonstrated that BDNF can cross the blood-brain barrier in both directions, via a high capacity saturable transporter system (Pan et al., 1998). Furthermore, it was reported that during physical exercise the increase in BDNF concentration in human was due to an enhanced release of BDNF from the brain (Rasmussen et al., 2009) suggesting that the blood level of BDNF may reflect the brain level.

Regarding the positive effect of cognitive training, the mechanisms involved have been examined in both animal models and humans. In animal models it was found that new learning promotes positive neuroplastic changes in the brain, associated with increased cerebral gray matter and hippocampal volume, and increasing learning capacity and synaptic density (Nithianantharajah and Hannan, 2006). Although these effects can be associated with increased BDNF production in brain neurons, it is also possible that other factors or mechanisms may be involved. For example, neurogenesis was also found to be linked to other factors besides BDNF, such as granulocyte colony stimulating factor while other studies also showed that cognitive activity not only promotes neuronal survival, but also increases the brain's vasculature (Thomas et al., 2012).

In humans, functional imaging and electroencephalography studies have also shown that improved cognition following cognitive training is associated with neuroplastic changes (Valenzuela et al., 2003) and neuroplasticity (Berry et al., 2010). Other biochemical changes associated with better neuropsychological performance in various cognitive domains, such as creatine and phosphocreatine signals, have been also observed in the hippocampus of healthy older individuals subjected to 5 weeks of focused memory training (Valenzuela et al., 2003). Furthermore, changes in the rate of cerebral glucose consumption were found in the brain of patients affected by amnesic mild cognitive impairments and subjected to cognitive training ( Förster et al., 2011).

These studies show that cognitive training may be beneficial in several neurodegenerative diseases. Although each of these diseases has certain characteristics that affect different areas of the brain with different outcomes, the common denominator is that the brain neurons undergo degeneration and subsequent death. In our study we found that these pos-
itive effects on PD patients were associated with increased BDNF serum levels. The past and present data clearly indicate that a deficit of neurotrophins is present in neurodegenerative diseases. Nevertheless, despite the discovery of the first growth factor, the nerve growth factor (NGF), dates back to the 1960s, we are still unable to exploit the potential of these proteins for the treatment of neurodegenerative diseases. The necessity to administer neurotrophins into the target region, bypassing the blood-brain barrier, has been a major obstacle to their use. Our study suggests an alternative endogenous way to increase these neuroprotective molecules in subjects affected by neurodegenerative diseases.

The potential benefits of an increase of neurotrophins in the brain after cognitive training may be that of delaying the onset and/or altering the progression of these diseases. This idea is supported by epidemiological studies which showed that the maintenance of an intense brain activity protects the brain from the onset of neurodegenerative disorders in old age. Various hypotheses have been proposed to interpret these findings. The “cognitive reserve hypothesis” was proposed to explain why individuals who engaged in higher levels of mental and physical activity were at a lower risk for developing dementia in later life (Ballesteros et al., 2015). Similarly, “the scaffolding theory of aging and cognition (STAC)” proposes that cognitive engagement, mental training, and exercise promote and strengthen scaffolding, a normal process present across the lifespan that involves development of complementary, alternative neural circuits to achieve a particular cognitive goal. The adaptive brain responds to the declines occurring in the neural structures and functional processes. In addition, it was also shown that the onset of other psychiatric disorders is reduced in classes culturally more developed. Regarding neurotrophins, it has been widely demonstrated that physical activity is able to increase brain levels of these proteins in laboratory animals and peripheral levels in humans.

In conclusion, the message we want to convey is that, since discovering the cause of a neurodegenerative disease revealed to be a difficult task, it is worth considering all possible forms of prevention. Among them, cognitive training represents a useful tool to prevent and/or delay the onset of neurodegenerative diseases, possibly increasing neuroprotective compounds such as members of the neurotrophin family. We feel that this area of research needs to be further developed, while waiting to find out the mechanism involved in the onset of these diseases.

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