Editorial

Aging Brain: In Search of Better Neurotherapeutics

The steadily increasing epidemiological prevalence of age-related neurodegenerative diseases and the deepening of knowledge on basic mechanisms underlying physiologic and pathologic aging processes of the brain account for the need of constant up to date of data emerging from fundamental, translational and clinical research.

Accordingly, original data from Bonfiglio et al. [1] offer a measure of the impact of environmental stimulation on the release of neurotransmitters (noradrenaline, glutamate and gamma amino butyric acid (GABA)) suggesting that these undergo different adaptations during aging and that they are differently tuned by “cognitive training”. The impact of “cognitive training” on neurotransmitter exocytosis might account for the cellular events involved in the reinforcement of “cognitive reserve” in both young and old animals. Although translation from rodent studies to clinical situation could be difficult, the results from pre-clinical models are of high clinical relevance, since they may allow a better understanding of the effects of environmental interventions in aging-associated chronic derangements in mammals. Also, they improve our understanding as to whether “cognitive training” promotes compensatory effects or, alternatively, if it elicits genuine recovery of neuronal defects.

There is no doubt that everyone experiences adverse events during life that impact both the health and quality of life. However, trajectories of health in aging can vary significantly depending on the individual. According to this hypothesis, Brivio et al. [2] envisage that a reduction of resilience may underlie an increased risk to develop pathological conditions during aging. In line with this idea, fragility in elderly would be the consequence of reduced function and responsiveness of biological systems, crucial for coping with stressful events. For the authors, it is therefore fundamental to identify and characterize the mechanisms that may contribute to the resilience or the vulnerability to stressful events, since such mechanisms may be significantly altered in the aged brain. However, a major gap in this field of research is that the studies are limited to assess molecular alterations under basal or resting conditions, without information on, if and how these functional impairments result in lack of stress responsiveness. The investigation of these mechanisms will be critical to identify genes and pathways the changes in which may contribute to achieve a better understanding of the risk architecture for age-related vulnerability and may represent potential targets for the development of novel pharmacological interventions.

In the above streamline of thoughts, Cerri and Blandini [3] report on dysregulation of the autophagic pathway as a contributing factor to PD pathogenesis via α-synuclein accumulation. Heterozygous mutations in the GBA1 (glucosylceramidase beta 1) gene are currently recognized as the most relevant risk factor for the disease pointing to lysosomal defects as major players in the PD-related impairment of the autophagic process. Preclinical findings support the use of therapeutic agents boosting autophagic activity, as potential disease-modifying agents. However, a deeper understanding of the mechanisms that may lead to autophagy defects in PD will be required to facilitate the design of new therapeutic interventions. The multifactorial nature of the disease allows this consideration to be extended to other mechanisms involved in PD pathogenesis, such as neuroinflammation oxidative stress, and mitochondrial defects.

Kustrimovic et al. [4] discuss the evidence accumulated supporting a fundamental role for neuroinflammation in PD; also, they originally contribute to the understanding of the active participation of peripheral immune mechanisms. The definition of the peculiar profile of CD4+ T naive and memory cells with likely consequent pro-inflammatory changes of immune system in PD patients suggests that these peripheral immune challenges can exacerbate the process of neuroinflammation and hence the symptoms of the disease also providing the rational basis for the proposal of immunotherapy for the treatment of PD.

Mancino et al. [5] demonstrate as the development of advanced neuroimaging techniques allows some degenerative diseases, considered of exclusive ocular relevance, to be associated with neurodegenerative phenomena of the Central Nervous System (CNS). Thus, a strong connection between the stage of glaucoma and alterations of the optic nerve and of the optic radiations has been assessed using diffusion tensor MRI (DT-MRI). In particular, with this
technique damage is measured by extrapolating from the images two numerical parameters: the Mean Diffusivity (MD) and the Fractional Anisotropy (FA). The finding showing increased values of MD and decreased values of FA, measured in the retrobulbar portions of the optic nerve of patients with glaucoma, suggests that also the extra bulbar portions of the optic nerve are affected by glaucoma. Interestingly, the analysis of DT-MRI parameter in glaucomatous patients at different stages of the disease showed that alterations in the early glaucoma are predominantly located at the level of retro-laminar region while, in the advanced stages, they also affect the distal portion of the nerve. Glaucomatous alterations may therefore be an expression of a neurodegenerative disease, which from the central areas extends to the retina. In this regard, recent studies using MRI reported that glaucoma affects not only the RGCs, but also the CNS with a similar mechanism found in other neurodegenerative diseases such as Alzheimer’s disease.

The latter disease accounts for approximately 50% of all cases of dementia and, in spite of the great effort, disease-modifying drugs are not available yet. Adherence to the current therapy of cognitive decline is needed for a better control of the disease and this is proven to reduce, though it does not abolish, the associated Behavioural and Psychological Symptoms of Dementia (BPSDs). On this aspect, Scuteri et al. [6] discuss how this cluster of symptoms, remarkably affecting patients’ health-related quality of life (HRQL), is tightly associated to pain states. Actually, antipsychotics are the only treatment for BPSDs though they are able to manage aggression but not agitation and they cannot control pain. Clinical trials with Melissa officinalis and Lavandula officinalis have demonstrated efficacy in handling BPSDs but strong evidence to offer relief from pain is lacking. At variance with the latter, Bergamot Essential Oil (BEO) is endowed with strong analgesic activity implicating pharmacological mechanisms, i.e., enhanced autophagy, a process undergoing derangement in chronic pain lending support to the pharmacological basis for clinical translation of aromatherapy with BEO in the treatment of BPSDs.

Altogether, the issue offers the perfect setting to discuss very interesting topics and to share studies and knowledge, thus widening our understanding of normal and diseased aging and giving rise to novel research lines for the development of better neurotherapeutics.

REFERENCES