Editorial

Neurons are typically post-mitotic cells. This means that they are expected to have a life span comparable to that of their carriers. Unfortunately, sometimes, they die prematurely as a result of complex processes known as “neurodegeneration”. Neurodegenerative diseases are now generally considered a group of disorders that seriously and progressively impair the functions of the nervous system through causing the selective neuronal vulnerability of specific brain regions. Neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer Disease (AD), Multiple Sclerosis (MS), and prion disease represent several distinct categories of disease and each manifests its own unique symptoms. However, the diseases share several common features, particularly the aggregation and deposition of abnormal proteins. Neurodegenerative disorders are associated with high morbidity, and few or no effective treatments have been available until now. Neurodegenerative diseases represent a threat to mankind in a variety of guises and induce chronic suffering and debilitation in about 2% of the worldwide population. Moreover, the increase in lifespan of western populations will mean that these neurodegenerative diseases will become more common. Consequently, it is estimated that the number of PD patients will double to between 8.7 and 9.3 million by 2030. As a group, these disorders are a major burden on health care systems compared with other causes of death and the costs of treatment are expected to rise sharply. Despite the enormous amount of progress we have made in terms of understanding the aetiologies of these diseases in the last few years, important questions remain unanswered. This special number deals with this hot topic and is produced by leading groups in the neuroscience field with the aim of summarizing recent advances in genetic, epideniological, molecular and cellular biology research that have increased our knowledge of the mechanisms that give rise to degenerative processes and, in general, to alterations of the structure and function of the nervous system. These contributions give insight into new pharmacological therapies for their treatment and review new and old drugs aimed at interrupting or at attenuating different pathogenic pathways of neurodegeneration and/or at ameliorating symptoms. The pharmaceutical industry faces arguably its most difficult challenge in attempting to develop therapeutics for neurodegenerative disease. The development of disease-modifying therapeutics that addresses the principal causes of neurodegenerative disease is still in its infancy.

de Lago and Fernández-Ruiz provide an extensive description of the neuroprotective properties of cannabinoids. They focus their review on the cellular and molecular mechanisms through which cannabinoids might arrest/delay the degeneration of specific neuronal subpopulations in neurodegenerative disorders such as PD, HD, multiple sclerosis (MS) and other motor-related disorders. The potential use of cannabinoid agonists as novel therapeutic options is based on their antioxidant, anti-inflammatory and anti-excitotoxic properties that allow them to afford neuroprotection in different disorders. Carnevale *et al*. review the current information on the reciprocal interactions between glia and neurons that are essential for many critical functions in brain health and disease. Microglial cells, the brain resident macrophages, and astrocytes, the most prevalent type of cell in brain, are actively involved in the control of neuronal activities both in developing and adult organisms. At the same time, neurons influence glial functions, through direct cell-to cell interactions as well as the release of soluble mediators. The authors concentrate on signals from neurons that may have an active role in controlling glial activation on two major neurotransmitters: acetylcholine (Ach) and noradrenaline (NA). The cholinergic and adrenergic anti-inflammatory pathways represent important physiological neuro-immune mechanisms by which the innate and adaptive immune responses are kept in control. The authors show evidence indicating that such mechanisms play a pivotal role in the inflammatory and immune processes within the CNS. ACh and NA appear to contribute with their pleiotropic functions to restrain glial activation and control inflammation and neurodegeneration. The development of specific agonists and compounds slowing the degradation of ACh and NA or their re-uptake might have therapeutic potential as anti-inflammatory agents for treating chronic neurodegenerative diseases.

A separate review by Pérez-De La Cruz *et al.* describes the catabolic route for tryptophan decomposition known as the kynurenine pathway. This is not only involved in different neurological disorders, but also possesses neuroactive metabolites with different biological properties, such as pro-oxidant and antioxidant regulators. They provide an overview on the relevance of this route for several disorders, and also add some further and recent information on the different biological properties of the neuroactive metabolites of this pathway and their significance for the design of potential therapies for those disorders involving excitotoxic, oxidative and inflammatory components.

Nunomura *et al.* review the role played by oxidative stress in the development and progression of AD and PD providing consistent evidence that oxidative insult is a significant early event in the pathological cascade of this disorder. Therefore they show that that pro-longevity gene products such as forkhead transcription factors and sirtuins are involved in the insulin-like signaling pathway and oxidative stress resistance against aging. An enhancement of the pro-longevity signaling (e.g. caloric restriction) may be a promising approach as anti-oxidative strategy against age-associated neurodegenerative diseases.

Unterberger and Voigtländer focused their paper on the pathogenic mechanisms of prion diseases. Prion diseases are rare fatal neurodegenerative disorders that may either occur sporadically, or be inherited or infectiously acquired in humans. Irrespective of aetiology, they can be transmitted to other individuals, this fact being responsible for the public attention prion diseases have received especially since the nineteen nineties, when a new variant of Creutzfeldt-Jakob disease linked to the consumption of prion contaminated beef occurred for the first time in Great Britain. In this review, they discuss actual and potential drug targets in the context of the pathogenic mechanisms of prion diseases.

The scenario that results from this special issue is that, despite the enormous research focused on neurodegenerative disorders, the underlying pathophysiology is not yet understood in sufficient detail. The situation is certainly a consequence of the complex interplay of genes, environment and their myriad interactions. There is not as yet a clear means of establishing efficacy in slowly progressing, late-onset disorders. Given the nature of these diseases, future therapeutics will need to be paired with tests for biomarkers indicating onset of brain pathology that precedes overt clinical symptoms. Therefore, it is of paramount importance to reveal those who are at high risk of developing these neurological disorders and allow them start an early program of prevention. This might involve a brain-healthy diet, very similar to a heart-healthy diet, and moderate physical activity with the aim of avoiding the other risk factors known so far.

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