

## Orexinergic neuron susceptibility to neuroinflammatory and aging-related neurodegenerative diseases

Giuseppe Bertini, Valeria Colavito, Amenutolera Wirtu, Marina Bentivoglio

Section of Anatomy and Histology, Department of Neurological and Movement Sciences, University of Verona, 37134 Verona, Italy

Orexins (a.k.a. hypocretins) play a crucial role in several physiological functions, including energy balance and the maintenance of wakefulness. Deficient orexin signalling is the hallmark of the sleep disorder narcolepsy. Although immune mechanisms have been hypothesized, the pathogenesis of narcolepsy remains to be clarified. Less attention has been devoted to potential orexinergic system alterations in other conditions, and their potential relationships with inflammatory signalling. Neuroinflammation has raised increasing interest in recent years, not only in relation to typical neuroinflammatory diseases, but also with regard to aging-related neurodegenerative diseases such as Alzheimer's and Parkinson's disease. A role for neuroinflammatory signalling in normal, "healthy" aging is also currently debated, since several lines of evidence have pointed to aging as a chronic low-grade proinflammatory condition. We have examined neurons in the lateral hypothalamus expressing orexin A in different paradigms: i) normal aging in mice, ii) rodent models of a chronic infectious neuroinflammatory condition represented by a parasitic disease that causes sleep/wake alterations, iii) PDAAP mutant mice, a model of Alzheimer's disease. In these paradigms, we have identified different degrees of neuronal loss in the orexinergic cell population and/or evidence of functional dysregulation of these neurons, together with glial activation in the lateral hypothalamus and sleep/wake changes. Altogether, the data point to a vulnerability of orexin to inflammatory signalling, and potentially place the neuropeptide at the center of neural-immune interactions, drawing attention on the relationships between neuroinflammation, sleep regulation, and orexin neuron damage.

### Keywords

Orexin, neuroinflammation, neurodegeneration, lateral hypothalamus, aging, Alzheimer's disease, Parkinson's disease.