

Introductory Remarks to Symposium 28

Early dysfunction of the locus coeruleus noradrenergic system in neurodegenerative diseases

Sabine Liebscher and Lars Paeger, Innsbruck (Austria) and Munich

The brainstem's Locus Coeruleus (LC) is the main noradrenergic (NA, or norepinephrinergic) nucleus and the sole source of NA to almost the entire forebrain. Through its complex afferents and efferent projections, the LC contributes to a vast number of physiological functions, including sleep-wake cycle, attention, arousal, memory formation, motivation, sensory processing and energy homeostasis. Early LC-NA degeneration is now widely accepted as a prominent feature of various neurodegenerative diseases and involved in a plethora of disease symptoms. The selective and early vulnerability of the NA system, however, remains a conundrum. Current work underscores the relevance of LC integrity as an early biomarker and offers critical insight into disease pathophysiology to identify novel therapeutic targets.

In this symposium we will present recent findings in rodents and humans linking LC- NA dysfunction to neurodegeneration typical of Alzheimer's disease (AD) and Amyotrophic lateral sclerosis (ALS). The session will feature latest research from Csaba Adori presenting unprecedented large-scale-3D cytoarchitectural analysis of the human LC covering tau-pathology stages Braak 0 to 6. Theresa Niedermeier will then demonstrate a link between tauopathy and *in vivo* mitochondrial transport deficits and functional deterioration in LC-NA axons in the cortex of mice.

Lars Paeger will share novel findings on the role of LC-NA system degeneration in the manifestation of early olfactory impairment in mice and humans in prodromal AD. As ageing is the most striking risk factor for dementia, Dorothea Hämmerer, will further discuss the possibility to image LC integrity in humans as a function of ageing and its relationship to cognitive performance. Evidence for a critical role of early, selective LC-NA dysfunction in humans and mouse models of another neurodegenerative disease, namely ALS, will be presented by Caroline Rouaux. Collectively, the symposium will highlight the crucial role of the NA system in neurodegeneration and will delineate its downstream cellular and network mechanisms, underlying disease symptoms and fueling the degenerative process *per se*.

Symposium 28

Friday, March 28, 2025
14:30 - 16:30, Lecture Hall 101

Chair: Sabine Liebscher and Lars Paeger,
Innsbruck (Austria) and Munich

- 14:30 Csaba Adori, Stockholm, Sweden
CYTOARCHITECTURE AND CELLULAR TAU PATHOLOGY OF THE HUMAN LOCUS COERULEUS – PERICOERULEAR COMPLEX REVEALED BY 3D IMAGING (S28-1)
- 14:55 Theresa Niedermeier, Munich
IN VIVO IMAGING OF MITOCHONDRIAL TRANSPORT ACROSS NEURONAL CELL TYPES REVEALS TAU-MEDIATED DYSFUNCTION IN THE LOCUS COERULEUS (S28-2)
- 15:10 Lars Paeger, Munich
EARLY LOCUS COERULEUS SYSTEM DEGENERATION UNDERLIES OLFACTORY DYSFUNCTION IN ALZHEIMER'S DISEASE (S28-3)
- 15:35 Dorothea Hämmerer, Innsbruck, Austria
PROBING THE NORADRENERGIC SYSTEM TO INVESTIGATE EARLY STAGES OF ALZHEIMER'S DISEASE (S28-4)
- 16:00 Caroline Rouaux, Strasbourg, France
LOCUS COERULEUS AND CENTRAL NORADRENALINE TARGETING TO COUNTERACT CORTICAL HYPEREXCITABILITY IN AMYOTROPHIC LATERAL SCLEROSIS (S28-5)
- 16:25 **Discussion and Concluding Remarks**