



ABSTRACT NO:ICCPPr-SPS-125

Intranasal Orexin Therapeutics for Sleep and Cognition: A Review of Pharmacological and Chronobiological Perspectives in Space Medicine

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Abstract

Astronauts on prolonged space missions experience profound sleep–wake disturbances due to microgravity, circadian desynchronization, and radiation exposure, leading to impaired cognition and reduced operational performance. Similar pathophysiological features are observed in terrestrial disorders such as narcolepsy, Alzheimer’s disease, and age-related cognitive decline, where current pharmacotherapies provide only partial benefit. This review highlights multidisciplinary approaches for mitigating circadian and cognitive dysfunction, including light-based entrainment, pharmacological modulation, gut–brain axis interventions, and complementary traditional practices. Particular emphasis is placed on the hypothalamic orexin (hypocretin) system, a central regulator of arousal, motivation, and memory. Intranasal administration of orexin-A peptides has emerged as a promising non-invasive strategy to bypass the blood–brain barrier and restore neural signaling. Preclinical evidence demonstrates enhanced cognitive resilience and reversal of sleep-related deficits with this approach. By integrating chronobiology, neuropharmacology, and innovative drug delivery, orexin-targeted therapeutics hold strong potential not only for space medicine but also for aging populations and neurodegenerative disease management on Earth.

Keywords: Orexin-A, Intranasal peptides, Sleep regulation, Cognitive resilience, Spaceflight countermeasures, Neurodegenerative disorders