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Author: Michihiro Mieda

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## ACCEPTED MANUSCRIPT

### The Roles of Orexins in Sleep/Wake Regulation

Michihiro Mieda

Department of Molecular Neuroscience and Integrative Physiology, Graduate School of Medical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8640, Japan.

#### Highlights

- Disruption of the orexin system causes the sleep disorder narcolepsy
- Orexin neurons stabilize wakefulness by promoting monoaminergic neurons
- Two orexin receptor subtypes differentially regulate sleep/wakefulness
- Orexin neurons suppress narcolepsy via at least two distinct efferent pathways
- Orexin neurons regulate wakefulness according to external and internal environment

#### **ABSTRACT**

Orexin A and orexin B are hypothalamic neuropeptides initially identified as endogenous ligands for two orphan G-protein coupled receptors (GPCRs). A deficiency of orexin signaling results in the sleep disorder narcolepsy-cataplexy in humans, dogs, and rodents, a sleep disorder characterized by excessive daytime sleepiness and cataplexy. Multiple approaches, including molecular genetic, electrophysiological,

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