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Converging orexinergic and reticular thalamic inputs on thalamic paraventricular neurons in normal conditions and experimental sleeping sickness

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A subset of excitatory neurons in the lateral hypothalamus, known to express the peptide orexin/hypocretin (Ox), play a key role in maintaining wakefulness. Projections from Ox neurons are widely distributed in the neuraxis but terminations are heavily concentrated in the thalamus along the midline, especially the paraventricular thalamic nucleus (PVT). The same areas receive afferents from inhibitory, GABAergic neurons expressing parvalbumin (Pv) in the thalamic reticular nucleus (Rt), which has long been considered essential for sleep regulation.

While the two circuitries have been regarded as distinct, we tested the hypothesis that PVT neurons represent a common target for both afferent systems by means of confocal microscopy of multiple immunofluorescence labeling in the mouse brain.

Calretinin (Cr) was used as marker of PVT neurons. Almost 90% of PVT perikarya were contacted by Pv+ terminals, confirming the prominent role of Rt in modulating PVT activity. Interestingly, about a third of these neurons were also reached by Ox+ terminals, suggesting a key role of the thalamic midline in integrating information pertaining vigilance state control. PVT cells receiving Ox+ but not Pv+ contacts were observed only rarely.

In mice infected with the parasite *Trypanosoma brucei brucei*, the causal agent of the neuroinflammatory disease "sleeping sickness", Pv+ afferents into PVT were largely preserved, while orexinergic fibers appeared fragmented and reduced in density. Importantly, the fraction of PVT perikarya receiving both Pv+ and Ox+ terminals was reduced by about 50%. The substantially decreased convergence of the two regulatory systems, in association with infection-induced disrupted sleep and sleep/wake cycles, further supports the hypothesis that PVT contributes to vigilance and arousal in physiological conditions.

Keywords

Neuroinflammation, diencephalon, African trypanosomiasis, immunofluorescence, confocal microscopy, orexin