This Week in The Journal

Cells That Trigger Arousal from Sleep When CO_2 Levels Rise

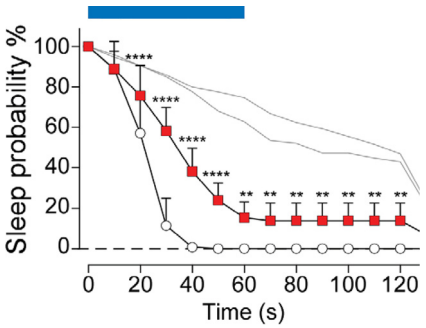
George M.P.R. Souza, Ruth L. Stornetta, Daniel S. Stornetta, Stephen B.G. Abbott, and Patrice G. Guyenet

(see pages 9725–9737)

Obstruction of breathing leads to a reduction in tissue oxygen levels (hypoxia) and an increase in CO_2 levels (hypercapnia). These conditions are detected by chemosensors in the brain and periphery, which in turn stimulate respiratory centers to increase the amplitude and frequency of ventilation. If hypoxia or hypercapnia occurs during sleep, they also trigger arousal so the obstruction can be removed. But whether arousal depends on the same chemosensory cells as increased ventilatory drive, and if so, whether arousal is stimulated directly by chemosensors or occurs downstream of effects on respiration remains unclear.

To address these questions, Souza et al. eliminated (in separate experiments) three groups of chemosensors previously shown to regulate ventilatory drive in rats, then asked how these manipulations affected arousal from sleep during hypoxia and hypercapnia. Removing the carotid bodies in the carotid arteries greatly reduced both the maximum change in ventilation volume and the probability that rats would awaken when chamber O_2 levels were reduced; it had a smaller effect on arousal and did not affect ventilation when CO_2 levels were raised. In contrast, ablating NK1R-expressing neurons in the brainstem retrotrapezoid nucleus (RTN) reduced changes in ventilation volume and the probability of arousal during hypercapnia, but did not affect breathing or arousal during hypoxia. Notably, the change in ventilation volume at the point of arousal in hypoxic and hypercapnic conditions was highly variable across trials and across rats, and it was lower in rats with RTN lesions than in controls. Finally, ablating cholinergic C1 neurons in the medulla had no effect on breathing or arousal during either hypoxia or hypercapnia.

These results suggest that the carotid bodies and RTN stimulate arousal from sleep as well as ventilatory drive in response to hypoxia and/or hypercapnia. In contrast, C1 neurons—which were previously shown to stimulate arousal and breathing—appear unnecessary to produce these effects in hypercapnic or hypoxic conditions. Although the results are consistent with the hypothesis that increases in ventilation effort contribute to arousal under hypoxia and hypercapnia, they suggest such increases are not necessary for arousal to occur. Investigating the targets of chemosensitive RTN neurons should elucidate how they trigger arousal when CO_2 levels are elevated.



Exposure to elevated CO_2 (blue bar) reduces the probability that normal rats (open circles) will remain asleep compared with when they breathe room air (gray traces). This effect is reduced by lesions to RTN (red squares). See Souza et al. for details.

A Mathematical Model of the GnRH Pulse Generator

Margaritis Voliotis, Xiao Feng Li, Ross De Burgh, Geffen Lass, Stafford L. Lightman, et al.

(see pages 9738–9747)

Reproductive organs are regulated by luteinizing hormone and follicle-stimulating hormone, which are released in pulses from the pituitary every 1–4 h throughout adulthood. These pulses are triggered by pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This, in turn, depends on synchronous activation of arcuate nucleus neurons that produce kisspeptin, neurokinin B (NKB), and dynorphin (KNDγ neurons). Whereas the release of kisspeptin from KNDγ neurons drives GnRH pulses, NKB and dynorphin provide positive and negative feedback, respectively, to the KNDγ network. Specifically, NKB depolarizes the neurons and dynorphin inhibits its NKB release. This feedback has been hypothesized to drive the periodic synchronous activation of KNDγ neurons that serves as the pulse generator for GnRH release (Herbison, 2018, Endocrinology 159:3723).

Voliotis, Li, De Burgh, et al. created a mathematical model that supports this hypothesis. The model describes changes in neuronal firing rate and NKB and dynorphin levels over time as the KNDγ network receives continuous excitatory input. Model simulations showed that short-term positive feedback provided by NKB created bistability in the network, causing it to shift between low- and high-activity states. Excitatory input above a threshold pushed the network from the low-activity to the high-activity state, after which dynorphin-mediated inhibition, which occurred with a slower time-course than NKB-mediated depolarization, returned the network to the low-activity state. Continuous excitatory input thus drove oscillations between the two states. As excitatory drive increased above the threshold, oscillations became faster, then slower, then ceased, returning the network to the basal state.

Importantly, the model accurately predicted how increasing optogenetic stimulation of KNDγ neurons *in vivo* would affect pulse generation, as measured by blood levels of luteinizing hormone. The model also predicted how blocking dynorphin and NKB signaling would affect pulse generation by the biological network: blocking dynorphin receptors lowered the stimulation threshold required for pulse generation, whereas blocking NKB receptors lowered pulse frequency.

These results support the hypothesis that positive and negative feedback within the KNDγ network contributes to pulse generation. They also suggest that pulse frequency is determined by the level of excitatory input to these neurons. Such input might be modulated by factors such as psychosocial stress and starvation, which may be how these stressors reduce fertility.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.39.49.2019.