

Astrocytes Play Key Role in Respiratory Center and Breathing Regulation

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Summary: A groundbreaking study from Karolinska Institute researchers reports astrocytes play a key role in the respiratory center of the brain stem and assist with the regulation of breathing. The findings are significant as they could provide clues to the causes of respiratory diseases.

Source: Karolinska Institute.

Star-shaped cells called astrocytes are much more than simple support cells in the brain. In a new study on mice, researchers at Karolinska Institutet demonstrate that they also play a key part in the respiratory centre of the brainstem and release inflammatory molecules that regulate breathing. The results, which are presented in the scientific journal *eLife*, can provide important clues as to the causes of respiratory disease and the sudden unexpected postnatal collapse of newborn infants (SUPC).

The control of breathing is essential for life. Without an adequate response to increased carbon dioxide levels, people can suffer from breathing disturbances, sickness, and panic. In a worst-case scenario, it can lead to premature death, as in sudden infant death syndrome. While it is known that respiration is regulated by the brainstem, just how this occurs remains very much a mystery. It is known that there are control mechanisms that cause the body to react to changing blood concentrations in CO₂, thereby preventing death. Eric Herlenius's research group at Karolinska Institutet

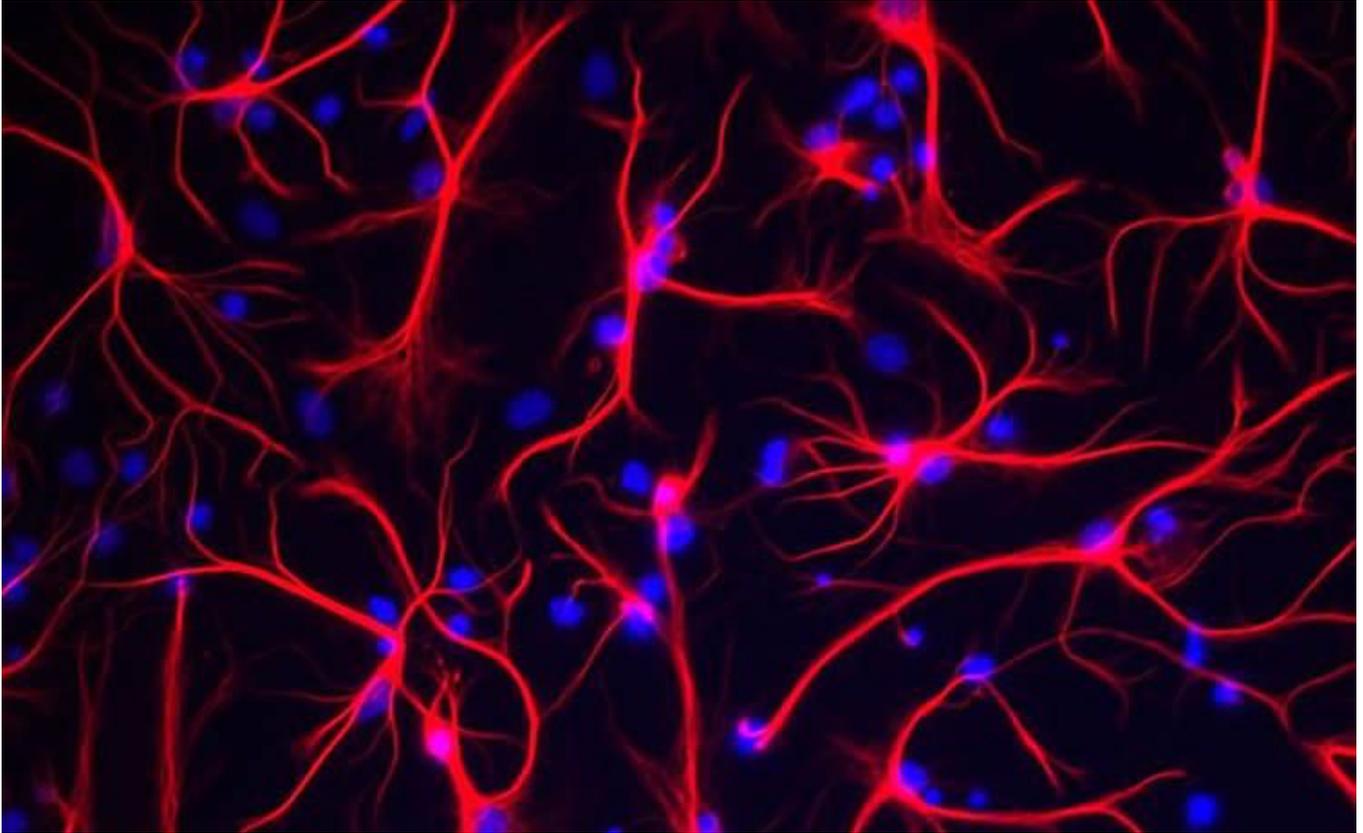
has previously shown that the molecule prostaglandin E2 (PGE₂), which is normally released during inflammation and fever, is triggered in the brainstem at high levels of CO₂, influencing the pattern and characteristics of respiration. The group has now shown that so-called non-neuronal astrocytes in the respiratory centre of the brainstem secrete this molecule.

“Astrocytes were once viewed just as a kind of glue that holds everything in place in the brain. Then they were considered as mere housekeepers providing structural and metabolic support for neurons. However, new research shows that they are involved in several vital processes, including respiration,” says Eric Herlenius, professor of paediatrics at the Department of Women’s and Children’s Health. “Our study shows that the astrocytes play an important part in the regulation of breathing by affecting the neurons and their network activity.”

To study the role of astrocytes in respiration, the researchers used an in-house developed technique in which part of the brainstem of a mouse is kept alive in a special culture dish. For several weeks neurons and astrocytes continue to be interconnected, and can transmit signals and generate rhythmic motor neuron activity as if they were “breathing”. The mice astrocytes were labelled with a fluorescent molecule, and contained a receptor that the researchers could stimulate in order to activate them. While most of the astrocytes seemed not to participate in rhythm generation, some of them formed their own functional network in the respiratory centre, displaying rhythmic activity similar to the neurons. These astrocytes integrated with the neurons, influencing their activity and consequently respiration.

“We knew that the astrocytes have the capacity of signalling just before inspiration but not that there’s this kind of connection from the astrocytes to the neurons,” says the study’s lead author David Forsberg, doctoral student at the same department. “Our hypothesis is that the astrocytes adjust the respiratory process with the help of the inflammatory molecule

PGE₂, and in doing so links breathing with the inflammatory system.”



To study the role of astrocytes in respiration, the researchers used an in-house developed technique in which part of the brainstem of a mouse is kept alive in a special culture dish. NeuroscienceNews.com image is credited to Archontia Kaminari.

Interestingly, the role of astrocytes seemed to differ between the two brainstem respiratory centres that were studied. In one, astrocyte activation caused an increase in neuronal activity, whilst in the other, neuronal activity remained unaffected. This suggests the presence of different types of astrocytes, and a diverse distribution of them in the brainstem.

Activation of the astrocytes also caused raised levels of PGE₂ and weakened the respiratory centre's reaction to high CO₂ concentrations, suggesting that the astrocytes become fatigued. Since PGE₂ is released during inflammation and fever, the researchers suggest that these conditions disrupt normal physiological reactions to CO₂, which can lead to potentially life-threatening breathing problems.

“We now want to find out if astrocyte fatigue can explain phenomena like SUPC, when newborn babies suddenly develop respiratory problems,” says Dr Forsberg. “Birth triggers a powerful stress reaction in the baby, which gives rise to high PGE2 levels. This has beneficial effects on newborns but we think this can be dangerous in combination with high levels of CO2.”

About this neuroscience research article

Funding: The study was financed by several bodies, including the Swedish Research Council, Stockholm County Council, Karolinska Institutet, the Swedish Brain Fund, the Marianne and Marcus Wallenberg Foundation and the Heart and Lung Foundation. Eric Herlenius is a coinventor of a patent application regarding biomarkers and their relation to breathing disorders. The other authors have not reported any competing interests.

Source: [Karolinska Institute](#)

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Abstract

Astrocytes release prostaglandin E2 to modify respiratory network activity

Previously (Forsberg et al., 2016), we revealed that prostaglandin E2 (PGE2), released during hypercapnic challenge, increases calcium oscillations in the chemosensitive parafacial respiratory group (pFRG/RTN). Here, we demonstrate that pFRG/RTN astrocytes are the PGE2 source. Two distinct astrocyte subtypes were found using transgenic mice expressing GFP and MrgA1 receptors in astrocytes. Although most astrocytes appeared dormant during time-lapse calcium imaging, a subgroup displayed persistent, rhythmic oscillating calcium activity. These active astrocytes formed a subnetwork within the respiratory network distinct from the neuronal network. Activation of exogenous MrgA1Rs expressed in astrocytes tripled astrocytic calcium oscillation frequency in both the preBötzinger complex and pFRG/RTN. However, neurons in the preBötC were unaffected, whereas neuronal calcium oscillatory frequency in pFRG/RTN doubled. Notably, astrocyte activation in pFRG/RTN triggered local PGE2 release and blunted the hypercapnic response. Thus, astrocytes play an active role in respiratory rhythm modulation, modifying respiratory-related behavior through PGE2 release in the pFRG/RTN.

“Astrocytes release prostaglandin E2 to modify respiratory network activity” by David Forsberg, Thomas Ringstedt, and Eric Herlenius in *eLife*. Published online October 4 2017 doi:10.7554/eLife.29566

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