Key component of respiratory center identified

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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."

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 CO_2, 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 CO_2."

More information: David Forsberg et al, Astrocytes release prostaglandin E2 to modify respiratory network activity, *eLife* (2017). DOI: 10.7554/eLife.29566

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