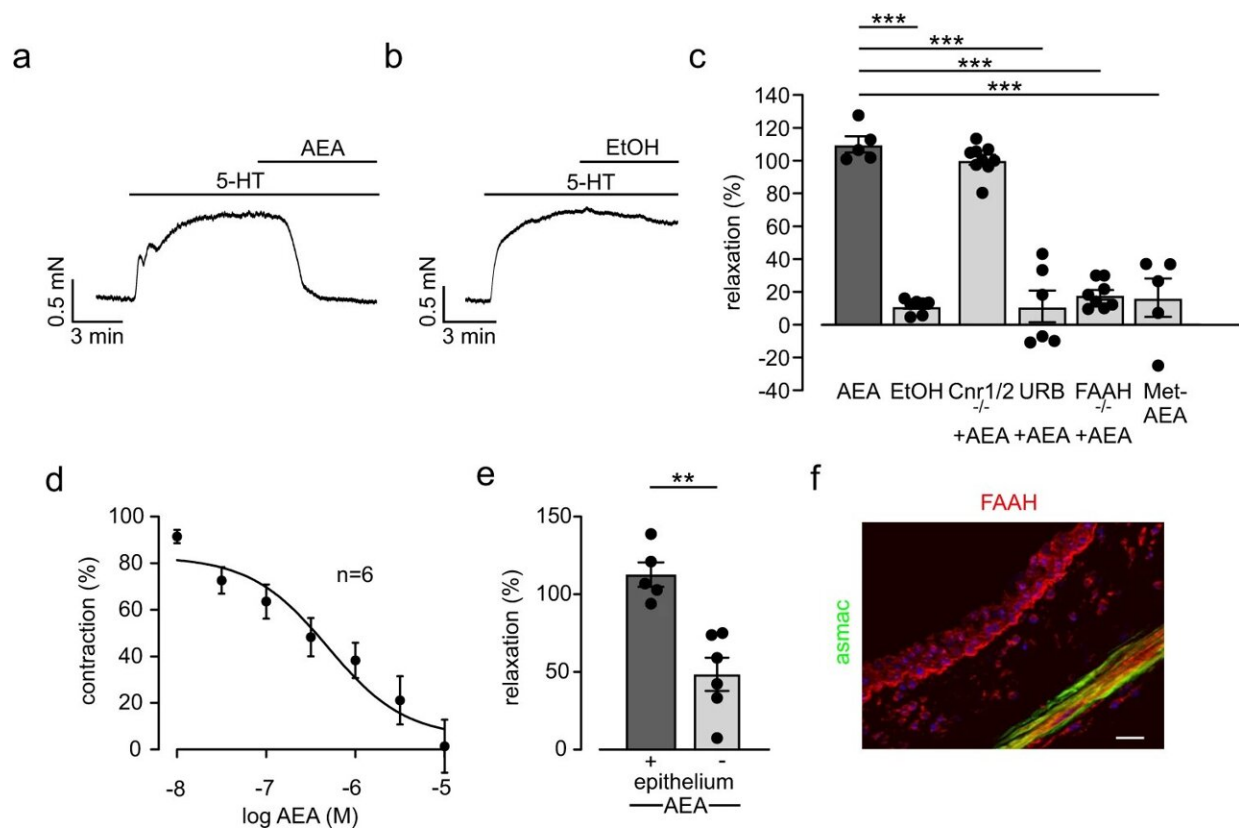


# How the body's own cannabinoids widen the bronchial tubes

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Anandamide (AEA) induces airway relaxation via fatty acid amide hydrolase (FAAH) in mouse trachea ex vivo. **a** Original trace of isometric force measurements in a myograph demonstrates strong tone decrease of tracheal ring from C57BL/6J mouse by a single dose of AEA (10  $\mu$ M). **b** Original trace of isometric force measurements shows no effect by application of the solvent ethanol (EtOH). **c** Statistical analysis of airway tone in response to AEA indicates that AEA ( $n = 5$ ) evokes relaxation independent from CB1 and CB2 receptors (Cnr1/Cnr2<sup>-/-</sup>,  $n = 9$ ); URB597 (URB, 1  $\mu$ M,  $n = 6$ ), methanandamide

(Met-AEA, 10  $\mu$ M,  $n = 5$ ); (EtOH,  $n = 7$ , FAAH<sup>-/-</sup>,  $n = 8$ ). Measurements were performed in independent samples. One way ANOVA, Tukey's post hoc test (AEA vs EtOH \*\*\* $p = 4.8 \times 10^{-12}$ ; AEA vs URB \*\*\* $p = 1.1 \times 10^{-11}$ ; AEA vs FAAH<sup>-/-</sup> \*\*\* $p = 1.6 \times 10^{-11}$ ; AEA vs Met-AEA \*\*\* $p = 1.5 \times 10^{-10}$ ). **d** Dose response curves of AEA from trachea of C57BL/6J mice ( $n = 6$  independent samples) show that the AEA-dependent airway relaxation is dose-dependent. **e** Statistical analysis of isometric force measurements demonstrates that the extent of airway relaxation by AEA (10  $\mu$ M) is different in tracheas with and without epithelium in C57BL/6J mice (+ $n = 5$ , - $n = 6$  independent samples), unpaired two-tailed Student's  $t$  test \*\* $p = 0.0012$ . **f** Immunostaining reveals FAAH expression in epithelial as well as smooth muscle cells of C57BL/6J mouse trachea (red = FAAH, green = alpha smooth muscle actin, staining was performed twice), scale bar = 20  $\mu$ m. **c–e**) Data are presented as mean values  $\pm$  SEM. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-34327-0

Bronchial constriction is what makes many lung diseases like asthma so dangerous. Researchers have discovered a new signaling pathway that causes the airways to widen.

Inhalation therapy for asthma and other obstructive lung diseases often loses its effect following prolonged use. A research team led by Professor Daniela Wenzel from the Department of Systems Physiology at Ruhr University Bochum, Germany, has now shown an alternative signaling pathway through which the body's own cannabinoids cause the bronchial tubes to dilate.

This gives rise to hope for alternative treatment options. Asthma is evidently also associated with a deficiency of these cannabinoids in the bronchial tubes, which could be one of the causes of the disease. The research team published its findings in *Nature Communications*.

## Bronchial tubes dilated by the body's own cannabinoids

Obstructive lung diseases are the third most common cause of death worldwide. They include [chronic obstructive pulmonary disease](#) (COPD), which affects many smokers, as well as bronchial asthma. During an [asthma attack](#), the bronchial tubes contract so violently that it is no longer possible to exhale—and this can be life-threatening.

"Asthma is an inflammatory process, but what is fatal is the constriction of the bronchial tubes," explains Annika Simon, lead author of the study. "This is why we are very much interested in the regulation of this constriction."

In a previous study, the researchers had likewise focused on the body's own [cannabinoid](#) system, specifically on its effect in the blood vessels of the lungs. The best known endogenous cannabinoid is anandamide. "Since our results show that anandamide dilates the bronchial tubes, we wanted to understand the exact mechanism behind it," explains Daniela Wenzel.

## Enzyme degrades cannabinoid

It quickly emerged that the two best-known receptors for anandamide (CB1 and CB2) are irrelevant for this regulation. Therefore, there must be an alternative signaling pathway through which the messenger substance anandamide acts on the bronchial tubes.

Daniela Wenzel and her team showed that this alternative pathway uses an enzyme called fatty acid amide hydrolase (FAAH). FAAH degrades anandamide, producing e.g. [arachidonic acid](#), which in turn is converted to prostaglandin E2. "We know that prostaglandin E2 can dilate the

bronchial tubes," says Annika Simon.

Prostaglandin E2 acts via certain receptors and leads to an increase in the messenger substance cAMP (cyclic adenosine monophosphate). "It is precisely this, the increase in cAMP, that is targeted by well-established inhalation medications against asthma," says Daniela Wenzel. So, the goal is the same, but the path is different.

## **Anandamide deficiency in asthma**

Wenzel and her team gradually deciphered the signaling pathway. They revealed that the enzyme FAAH is located both in the smooth muscle of the bronchial tubes and in the ciliated epithelium. The increase in cAMP after anandamide administration could be detected both in the [mouse model](#) and in human bronchial cells. In order to find out whether anandamide could also work in asthma patients, the team used a disease model in mice where certain substances can be used to create artificial asthma.

In these animals, too, the administration of anandamide led to a widening of the bronchial tubes. "This means that [asthma](#) doesn't result in resistance to anandamide," explains Daniela Wenzel. Moreover, the researchers found that asthmatic animals have less anandamide and other endocannabinoids in their bronchial system than healthy animals. "Therefore, it's possible that this [anandamide](#) deficiency is one of the causes of [bronchial asthma](#)," concludes Daniela Wenzel.

The discovery of the new signaling pathway could also open up new possibilities for intervening in the disease process. "But there's still a long way to go, and it will certainly take several years," says Daniela Wenzel. She expressly warns patients not to undertake experiments with cannabis plants.

"We can't draw any direct conclusions regarding plant cannabinoids from the findings on endogenous cannabinoids. Exactly which other ingredients are found in cannabis plants besides the known cannabinoids is entirely unclear. Plus, the plants sometimes contain harmful substances."

Nevertheless, the findings of this study are already pointing towards a better understanding of the body's own cannabinoid system, which could lead to new treatment options for [lung diseases](#) in a few years' time.

**More information:** Annika Simon et al, The endocannabinoid anandamide is an airway relaxant in health and disease, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-34327-0](https://doi.org/10.1038/s41467-022-34327-0)

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