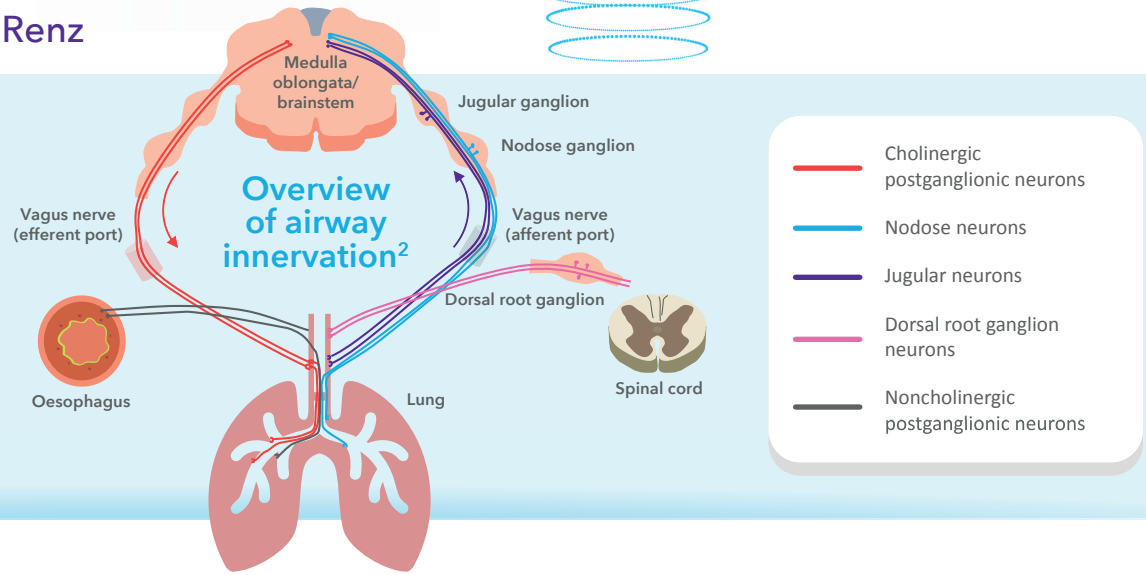
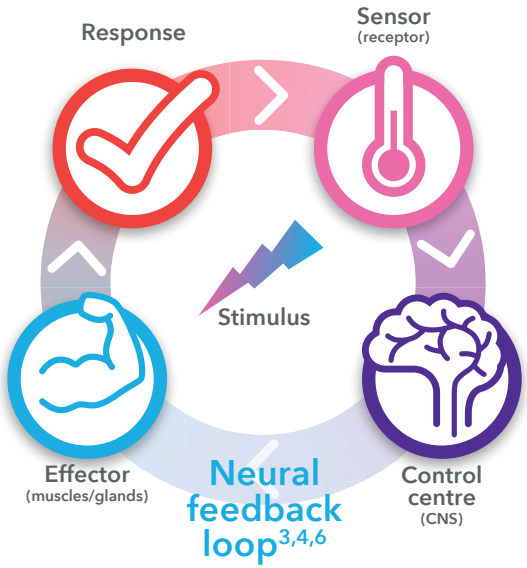
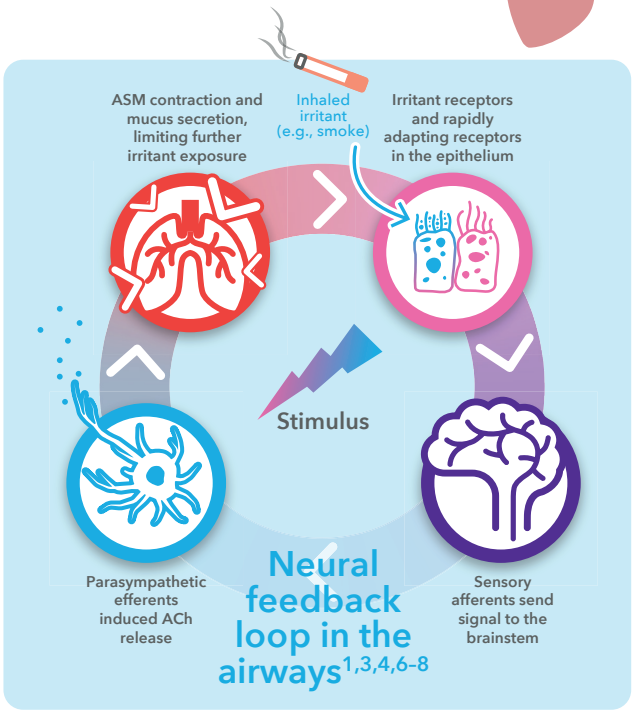
Neuroinflammation in airway diseases

Developed in collaboration with Professor Harald Renz

- The airways are innervated by a dense network of parasympathetic, sympathetic and sensory nerves, that are essential for breathing regulation, but also drive bronchoconstriction and mucus secretion[1,2]
- Airway innervation also provides the basis for the initiation of defence mechanisms in response to viral and bacterial infection and environmental irritants[2]







- The nervous system functions in a regulatory feedback loop between the brain and different organs (e.g., lungs, gut, skin), and maintains homeostasis by constantly monitoring and adjusting to changes[1,3,4]
- The airway epithelium anatomically and functionally collaborates with the nervous system[5]
- In inflammatory airway diseases, such as asthma, the neural feedback loop is amplified in response to repeated exposure to triggers[9–13]
  - Leading to pathological features, e.g., airway hyperresponsiveness and exaggerated inflammatory response[11,12]

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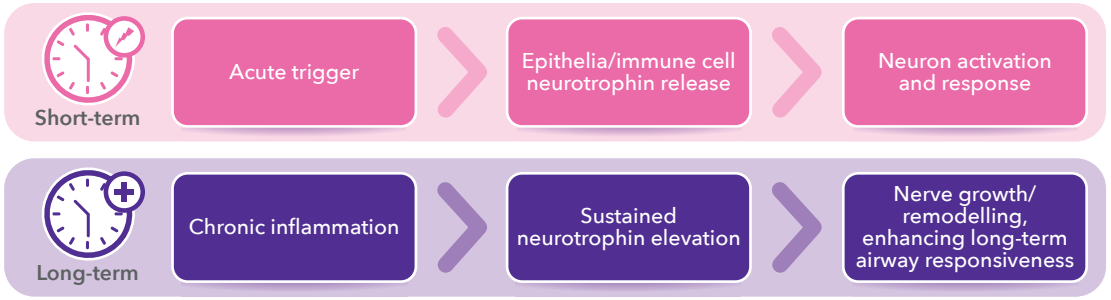
Neuroinflammation in airway diseases

Acute triggers and chronic inflammation drive different short- and long-term neural responses in the lungs[14–20]



- Airway epithelial, immune and structural cells produce neurotrophins, e.g., NGF and BDNF[19]
  - Patients with asthma have higher baseline levels of NGF and BDNF expression compared with individuals who do not have asthma[14,17,21]
  - Sustained NGF and BDNF levels in asthma cause increased nerve density and persistent AHR[12,17,20]
- T2 alarmins produced by the epithelium (e.g., IL-33, TSLP) can also stimulate sensory neurons[2]
  - TSLP and IL-33 are epithelial cytokines that are released by activated epithelial cells in response to injury or immunological insult[22,23]

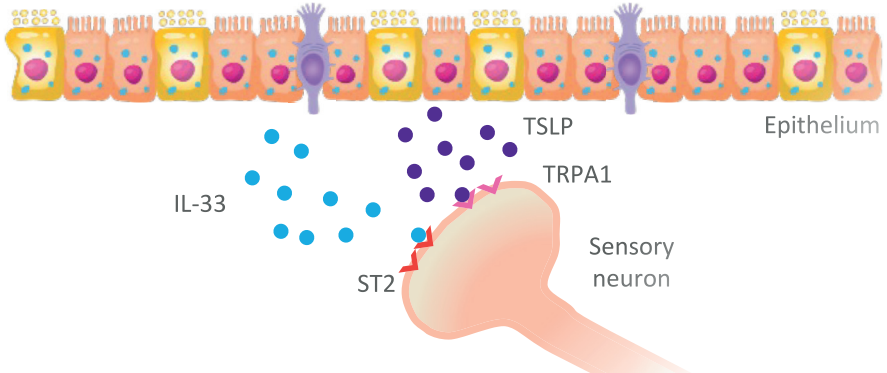
IL-33

- IL-33 can stimulate sensory neurons directly through ST2 expressed in small-diameter sensory neurons[2]
  - This IL-33/ST2 axis has been shown to drive inflammation and pathophysiology in patients with asthma[2]
- Outside of the lungs, IL-33 has been shown to directly activate peripheral sensory neurons via ST2[24,25]
  - In dry skin, IL-33 signalling in sensory neurons drives chronic itch, but with minimal inflammation[25]

TSLP

- In the skin, TSLP has been shown to activate a subset of TRPV1+ and TRPA1+ sensory neurons[2,26]
  - TSLP binds to its receptor on the neuron, activating phospholipase C signalling, which couples MrgprC11 to TRPA1, and Gβγ, which couples MrgprA3 to TRPA1. Both processes excite the neuron[2,26]
- TRPA1 activation promotes lung inflammation in mouse models of airway inflammation and asthma[26]
  - Elevated epithelial TSLP in asthma is associated with airway inflammation and AHR[27]

Epithelial cytokine interaction with sensory neurons[2]



ACh, acetylcholine; AHR, airway hyperresponsiveness; ASM, airway smooth muscle; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; IL, interleukin; NGF, nerve growth factor; ST, growth stimulation expressed gene; TRPA, transient receptor potential ankyrin; TRPV, transient receptor potential vanilloid; TSLP, thymic stromal lymphopoietin; T2, type 2.

1. Voisin T, et al. *Int Immunol*. 2017;29(6):247–61; 2. Nassenstein C, et al. *J Allergy Clin Immunol*. 2018;142(5):1415-22; 3. Hall JE and Hall ME. *Guyton and Hall Textbook of Medical Physiology*. 14th ed. Philadelphia: Elsevier; 2020; 4. Kandel ER, et al. *Principles of Neural Science*. 5th ed. New York: McGraw-Hill; 2013; 5. Czerwaty K, et al. *Diagnostics* (Basel). 2022;12(10):2361; 6. Audrit KJ, et al. *Cell Tissue Res*. 2017;367(3):571–90; 7. Piedimonte G. *Respir Res*. 2002;3 Suppl. 1(Suppl. 1):S21–S25; 8. Widdicombe JG. *Respir Physiol*. 2001;125(1–2):3–15; 9. Trevizan-Bau P and Mazzone SB. *Ann Allergy Asthma Immunol*. 2023;131(5):550-60; 10. Su Y, et al. *Nature*. 2024;631(8021):601–9; 11. Wu W, et al. *Respir Res*. 2024;25(1):83; 12. Pincus AB, et al. *Neurosci Lett*. 2021;751:135795; 13. Pavón-Romero GF, et al. *Front Cell Dev Biol*. 2021;9:663535; 14. Frossard N, et al. *Eur J Pharmacol*. 2004;500(1–3):453–65; 15. Nockher WA and Renz H. *J Allergy Clin Immunol*. 2006;117(1):67–71; 16. Renz H. *Respir Res*. 2001;2(5):265–8; 17. Prakash Y, et al. *Expert Rev Respir Med*. 2010;4(3):395–411; 18. Freeman MR, et al. *Am J Physiol Lung Cell Mol Physiol*. 2017;313(2):L360–L370; 19. Hahn C, et al. *J Allergy Clin Immunol*. 2006;117(4):787–94; 20. Drake MG, et al. *Front Physiol*. 2021;12:720538; 21. Watanabe T, et al. *Am J Respir Cell Mol Biol*. 2015;53(6):844–52; 22. Bartemes KR and Kita H. *Clin Immunol*. 2012;143(3):222–35; 23. Gauvreau GM, et al. *Expert Opin Ther Targets*. 2020;24(8):777–92; 24. Liu B, et al. *Proc Natl Acad Sci U S A*. 2016;113(47):E7572–E7579; 25. Trier AM, et al. *J Allergy Clin Immunol*. 2022;149(4):1473–80.e6; 26. Wilson SR, et al. *Cell*. 2013;155(2):285–95; 27. Andreasson LM, et al. *J Allergy Clin Immunol*. 2024;153(4):988–97.e11.

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