It was discovered in the early 1900s that CO2 provides a major drive for breathing, part of a homeostatic reflex to eliminate CO2 and regulate pH in the brain and body. The location of the neuronal sensors that mediate this chemosensory reflex, and the mechanisms by which those neurons detect changes in CO2 and/or pH have been elusive. This talk will describe salient findings from a series of studies over the last decade that have identified the relevant chemosensitive neurons in the caudal brainstem, and uncovered distinct molecular proton detectors that regulate their excitability to drive breathing.