Salivary gland function is essential for oral and general health. Autonomic input to salivary glands rapidly and dynamically controls the rate of salivary flow by the coordinated activities of ion channels and transporters that induce water movement and promote the exocytotic secretion of digestive enzyme and other proteins. This control is achieved by mechanisms that generate complex patterns of cytosolic calcium. Diminished saliva production, or dry mouth, has a profound impact on quality of life. Although patients can benefit from treatments that stimulate residual secretory capacity, current treatments generally provide only temporary relief. Using a variety of biochemical, optical, and electrophysiological approaches, we identified novel cell signals that stimulate salivation and point to potential new targets for augmenting or restoring function for patients suffering reduced saliva formation.