Carbonic Anhydrases: Dissimilar protein structures but similar functional roles in taste, smell and neuronal activity

Carbonic anhydrases (CA) are a family of enzymes which have multiple physiological roles. Their initial role was to preserve systemic acid-base balance through their activity to enhance the reaction $\text{H}_2\text{O} + \text{CO}_2 \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^\text{−}$.

There are multiple CAs. Each has an unique protein structure with unique physiological activities. However, each enzyme has a similar active site containing one zinc atom, two histidine atoms and one H$_2$O molecule. Each CA is found in specific tissues. Each exhibits specific functional activities in addition to roles in the reaction which produced H$^+$ + HCO$_3^\text{−}$. These activities vary greatly. However, as shown in March What's New several of the CAs (CA I, II, IV and VI) have been shown to play some role in taste and smell function.

Initial understanding of the roles these enzymes play in sensory function was discovered following discovery of clinical abnormalities associated with sensory changes in taste or smell observed in absence or decreased secretion of these enzymes.

Patients with decreased gustin [carbonic anhydrase (CA) VI] in saliva or nasal mucus exhibited loss of taste and smell, respectively. CA VI is the only secreted CA. In humans secretion of CA VI from serous glands in the nose goes directly into nasal mucus which supports smell function. CA VI is also found in parotid glands in the mouth; it is secreted by these glands directly into saliva to support taste function. CA VI has been found in both taste bud cells and in cells of the olfactory epithelium. When CA VI is secreted into the mouth or into the nose it is “directed” to taste buds or olfactory epithelium where it is delivered from saliva or nasal mucus, respectively.

CA VI depletion in saliva or nasal mucus causes CA VI depletion in taste buds or olfactory epithelium and is the basis for taste and smell loss. Since zinc is at the active site of all CAs any process which causes zinc depletion inactivates this enzyme. If zinc is removed from CA VI zinc is depleted from taste buds and olfactory epithelium thereby inducing taste and smell loss. Dietary zinc depletion in animals and in humans causes taste loss. Zinc malabsorption in humans related to several pathologies including Crohn’s disease and Sprue causes taste loss. Since zinc is the critical cofactor in CA VI zinc administration to patients with impaired taste and smell enhance its synthesis. Increased secretion of CA VI in saliva and nasal mucus restores both smell and taste function.

Patients with CA II deficiency exhibit multiple somatic abnormalities. Loss of smell has been reported as part of the panoply of these abnormalities. These patients, usually children, have intellectual deficiencies which make reports of their loss difficult to interpret and any response to treatment difficult to understand.

Both CA I and CA II have been found in taste buds in animals but has not been identified in humans.

CA IV, a membrane bound CA. It has been found in taste buds in animals. CA IV activity has been associated with loss of taste for CO$_2$ in humans. This taste is associated with perception of the taste of carbonated beverages. Depletion of CA IV in animals has been associated with loss of this taste ability. CA IV have also been reported to be a marker associated with the blood-brain barrier (BBB). The BBB acts as a gate to substances entering the brain from the peripheral circulation. CA IV has also been discovered in the human eye.
How do these enzymes which are structurally so different play a role in taste and smell function?

CA activity has been found in many tissues. These include not only taste buds and olfactory epithelium but also primary sensory nerves and cranial nerve efferent neurons. These studies suggest that CAs not only play a role in taste and smell function but also in neuronal function.

Despite their dissimilar protein structure actions of these various CAs supporting taste and smell may lie in their neuronal functional similarities. While these similarities have not been evaluated systematically they may lie in their hypothesized similarity to act as nerve growth factors (NGF).

NGF is a protein which initially was discovered to support sympathetic ganglion cell growth and cause axonal sprouting or specific neuronal growth. Placing NGF on sympathetic ganglion cells actually caused these cells to grow, develop and sprout nerve processes. NGF was subsequently discovered to play many roles as a growth factor in several neuronal tissues.

Because CA VI acts in taste buds and olfactory epithelium it has been labeled a “growth factor” which causes taste buds and olfactory epithelium to grow. In some studies we have done CA VI has been shown to act directly like NGF.

In isolated purified taste bud receptor membranes CA VI has been shown to inhibit and reverse the binding of NGF to these membranes. This binding of NGF was specifically inhibited and reversed by addition of CA VI. In a similar set of studies using cultured PC12 cells binding of NGF to these cells was specifically inhibited and reversed by addition of CA VI just as it was with taste bud cells.

However, while these similarities between CA VI and NGF exist there are also differences in the action of NGF and CA VI. While NGF maintained both cellular growth and caused axonal sprouting in sympathetic ganglion cells CA VI only maintained cellular growth without causing axonal sprouting. NGF also activated growth of cultured PC12 cells and axonal sprouting whereas CA VI only maintained growth of these cells. These studies indicate some functional similarity between CA VI and NGF which is incomplete. CA VI also activates calmodulin dependent brain phosphodiesterase activity which related CA VI to adenylyl cyclase and cAMP activity. Adenylyl cyclase has been shown to enhance neuronal growth in cultured neurons and to play an important role as a growth factor in taste buds and olfactory epithelium.

These studies suggest that CA VI has activity similar to NGF and can act in some way similar to adenylyl cyclase. Perhaps the other structurally different disparate CA enzymes, CA I, II, IV, play a role similar to NGF. Perhaps each CA may also act as a growth factor to initiate cellular growth in the nervous system.

References:


