sweetness? Two possibilities present themselves. One, not tested here, is a reduction in mixture suppression (Kiesow, 1896). This well-studied phenomenon occurs when compounds eliciting different taste qualities (e.g., sweet versus bitter or sweet versus salty) are perceived as being less intense when mixed together than when tasted separately. By inhibiting the ability of each other to activate TAS2Rs, the perceived bitterness of saccharin and cyclamate is reduced, and thus, perceived sweetness may be less suppressed. An alternative (though not mutually exclusive) possibility is that the coincident binding of saccharin and cyclamate to the sweet taste receptor results in increased activation. Behrens et al. (2017) tested this directly by comparing the activation of TAS1R2 + TAS1R3 by saccharin-cyclamate mixtures to that elicited by either sweetener alone. No change was seen in efficacy, indicating that synergistic taste responses to these sweeteners is not a result of enhanced sweet taste receptor activation. A slight leftward shift of the concentration-response curve for the sweetener blend suggests the possibility of increased potency, but the significance of this shift to taste perception is unclear. Therefore, it appears that inhibition of bitter taste receptors, rather than increased activation of the sweet taste receptor, best explains the enhanced sweet perception observed with saccharin-cyclamate mixtures.

The use of a few prototypical stimuli that evoke distinct perceptual qualities (e.g., sucrose for sweet, quinine for bitter) has been critical for unraveling the neural mechanisms underlying taste. However, we rarely experience pure taste stimuli. Rather, they are encountered as components of complex mixtures—usually in the form of food or drink—and in the context of texture, temperature, odors, and other sensory signals. As this study shows, it is possible to gain insights into complex sensory phenomena through targeted mechanistic studies. Researchers exploring the roles of receptors and sensory cells in taste function would be wise to extend their studies beyond individual stimuli. You might just have to mix it up a bit.

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Nanoscale Imaging Reveals Big Role for Iron in Alzheimer's Disease

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In this issue of *Cell Chemical Biology*, Telling et al. (2017) apply advanced X-ray microscopy techniques to reveal magnetite iron species in plaques from a mouse model of Alzheimer's disease. The characterization of abnormal iron chemistry in the disease model highlights the potential for iron to combine with the β-amyloid peptide and accelerate the disease process.

The β-amyloid peptide (Aβ) is a natural product of sequential processing of the β-amyloid precursor protein. While ordinarily present in the human brain, Aβ can oligomerize and deposit in plaque as the defining pathological feature of Alzheimer's disease. The pathological processes that drive Aβ down the amyloidogenic pathway are undefined but may present as therapeutic targets to stop the disease process.

Metal ions such as iron have been shown to greatly accelerate oligomerization of Aβ using *in vitro* assays (Huang et al., 1999). While these assays reveal the potential for a pathological role of iron in driving the disease process,

the demonstration of iron accelerating pathology accumulation in an *in vivo* setting has proven more elusive. In mouse models, iron treatment exacerbates pathology accumulation (Becerril-Ortega et al., 2014), while removing iron with iron chelator drugs reduces pathology severity (Sripetchwandee et al., 2016). In a recent longitudinal biomarker study, elevated CSF ferritin (reporting brain iron) predicted accelerated depreciation of $A\beta_{1-42}$ in CSF (reporting increased plaque formation) (Ayton et al., 2017a). While these *in vivo* studies support a role for iron promoting amyloid accumulation, it cannot be excluded that iron participated upstream of this process by increasing translation and processing of APP, leading to increased abundance of the peptide available for aggregation.

However, co-localization studies of iron and amyloid present as ''smoking gun'' evidence that iron indeed participates in the accumulation of pathology. In living patients, mixed-modality MRI and PET imaging studies show high iron levels in brain areas where plaque is also elevated (Ayton et al., 2017b). In post-mortem studies, which provide greater spatial resolution, iron has been shown to be associated with plaque by immunohistochemistry (Smith et al., 1997) and by MRI transverse relaxation of brain slices (Meadowcroft et al., 2015). Similarly, James et al. (2017) have demonstrated that iron is associated with the majority of the plaques deposited in the brains of in APP/PS1 mice using X-ray fluorescence. However, until recently, the chemical composition of iron associated with plaque has not been convincingly described. By using advanced electron microscopy techniques, Plascencia-Villa et al. (2016) have revealed mineralized iron in the form of magnetite nanoparticles in Aβ plaque cores from post-mortem cases of Alzheimer's disease. Since magnetite is not a normal feature of the human brain, the enrichment of this mineral suggested that aberrant iron redox chemistry impacts the disease.

In this issue of *Cell Chemical Biology*, Telling et al. (2017) now extend upon this work by applying advanced X-ray microscopy techniques to also reveal elevated amounts of reduced ferrous iron and deposits of magnetite associated with plaques from the APP/PS1 mouse model of Alzheimer's disease. Scanning X-ray microscopy (STXM), which combines high-resolution microscopy with sensitive spectroscopy, was used to map the extent of protein aggregates and speciation of iron in tissue sections, quantifying iron oxidation state at nanoscale resolution. The cortex of APP/PS1 transgenic mice exhibited abundant iron deposits that co-localized with amyloid structures. Importantly, very few iron deposits were identified in cortical sections of wild-type mice.

Telling et al. (2017) then went on to characterize the magnetic properties of these iron deposits using X-ray magnetic circular dichroism (XMCD), and they were found to mirror the magnetic properties of magnetite, consistent with the work of Plascencia-Villa et al. (2016). Telling et al. extend this finding by revealing substantial levels of ferrous (Fe^{2+}) iron; indeed, within the polyphasic iron deposits, they detected regions of almost pure Fe^{2+}. The presence of enriched Fe^{2+} could present as a potent source of free radical generation, since Fe^{2+} is the catalyst for the Fenton reaction, which generates the highly reactive hydroxyl radical. It is also possible that the Aβ present in the plaque acts to reduce Fe^{3+} to Fe^{2+} (as has been shown *in vitro* [Huang et al., 1999]), thereby actively participating in the mineral deposition.

Telling et al. (2017) report amyloid-iron composites in diffuse amyloid deposits. Diffuse plaques historically have been considered to be immature plaque lesions, so this finding indicates that iron might combine with amyloid in the initial stages of plaque genesis. The observation that iron is enriched in amyloid deposits is consistent with the potential for iron to accelerate the aggregation of Aβ, as has been previously shown *in vitro* (Huang et al., 1999) and using Alzheimer disease animal models *in vivo* (Becerril-Ortega et al., 2014; Sripetchwandee et al., 2016).

So, could iron initiate amyloid plaque formation? Evidence from the genetic disease class termed neurodegeneration with brain iron accumulation (NBIA) suggests not. In a survey of brain pathology in post-mortem cases of NBIA, amyloid plaque was not identified as a common pathological feature (Kruer, 2013). Since the defining feature of NBIA cases is pathological brain iron accumulation, yet amyloid plaque is not a feature, this suggests that tissue iron elevation itself does not induce normal Aβ to deposit. Recent data have revealed that higher CSF ferritin is associated with accelerated plaque formation only in people with underlying amyloid pathology and not in people where amyloid pathology is minimal (Ayton et al., 2017a). This also suggests that iron acts to accelerate amyloid accumulation but may not be the seeding factor for amyloidogenesis.

The work by Telling et al. (2017) contextualizes the nanoscale chemistry of iron within that most classic pathological hallmark of neurodegenerative disease, the amyloid plaque. The fine scale nature of this work provides a most welcome *in situ* view of iron biochemistry that has been lacking. The application of techniques able to probe the magnetic sub-structure within iron deposits, only microns in size, revealed unappreciated heterogeneity in the chemistry of iron oxides in close association with amyloid. This type of highly focused analysis hints at a complex, structural relationship between the formation/maturation of cerebral amyloid deposits and the redox chemistry of iron. This type of finding reinforces the rationale for trialing compounds that modulate brain iron, or iron-oxidative chemistry, for potential therapeutic benefit for Alzheimer's disease.

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