Oleocanthal: A story of discovery

Gary K. Beauchamp
Monell Chemical Senses Center
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Sometimes a very specific question from one of Monell' Sponsors can lead to research programs that provide insights into fundamental problems in flavor biology. Our discoveries surrounding the anti-inflammatory compound oleocanthal, a compound with unusual perceptual properties, provides one dramatic example of this.

A number of years ago, Reckett Benckiser (RB), a Monell Sponsor company, asked us whether we could help them understand why they were having so many taste complaints from consumers regarding an over-the-counter cold remedy. This liquid-based formulation had recently been upgraded by adding ibuprofen, the non-steroidal anti-inflammatory pain reliever, as an ingredient and we assumed that the complaints must involve the perceptual properties of ibuprofen about which little were known.

Although Monell does not work on specific products unless such work raises a basic research question, we were intrigued with the observation and agreed to "taste" the new formulation. When we did, we immediately recognized that the problem was not with taste (that is sweet, sour, salty, bitter or umami) but that ibuprofen caused a very distinctive and unpleasant irritation that was restricted almost exclusively to the throat. This interested us from a scientific perspective because it was not clear what the mechanism of this throat-restricted irritation might be. Most irritants such as capsaicin (the active irritant in hot peppers) irritate the entire oral cavity. Thus the question was why did ibuprofen only irritate the throat? We wondered whether it might activate an unknown receptor found in the throat but not in the mouth.

Consequently, we engaged in a research collaboration with RB to understand more about the sensory basis for this unusual percept. This project resulted in a scientific publication by two of my colleagues, Paul Breslin and Barry Green, showing that the irritation was indeed highly restricted to the throat and that it was pH sensitive, thereby providing RB with an approach to reduce the unpleasant sensation. But we remained puzzled by the strange localization of the irritation to the throat and hoped we would have a chance sometime to investigate its mechanism.

Independently, and at about this same time, I was attending a meeting on Molecular Gastronomy in Italy where scientists, chefs and journalists explored the science behind cooking and food choice. Here I was introduced to sensory evaluation of extra virgin olive oils (EVOO). Procedures were essentially the same as for wine – smelling the volatiles coming from a wine glass with small amount of oil, sipping it, and then swallowing it. We had the opportunity to sample a particularly fresh batch of very high quality extra virgin olive oil from a local olive grove. I swallowed it and was startled to experience what appeared to be an identical throat burning sensation to that I had experienced when I swallowed liquid ibuprofen.

This led me almost instantaneously to the hypothesis that high quality EVOOs may contain a compound that mimics not only the sensory properties of ibuprofen, but perhaps also has similar pharmaceutical actions. This hypothesis was based on ideas put forward over half a century ago by Roland Fisher who suggested that the oral cavity might act as an in situ pharmacological sensor. Flavor sensitivity and drug sensitivity may be tightly

connected he speculated. And if EVOO did contain a natural anti-inflammatory compound, then it was possible that some of the health benefits of the Mediterranean diet, which include lower rates of cardiovascular disease, some cancers and neurodegenerative diseases such as Alzheimer's, were a consequence of the regular ingestion of low levels of this hypothesized natural anti-inflammatory compound. This made sense since there is some evidence that long-term consumption of ibuprofen has the same beneficial effects against these diseases as does the Mediterranean diet.

The hypothesis that EVOO contains a natural anti-inflammatory compound and that this compound is responsible for the unusual throat burn was tested at Monell in a wide-ranging collaboration that included another Monell sponsor, Firmenich. In 2005, Monell published a report in the scientific journal Nature that verified this hypothesis and also identified the compound responsible, oleocanthal. Although oleocanthal (so named by us as follows: Oleo = olive; canth = sting; al = aldehyde) is not chemically related to ibuprofen, its sensory properties allowed us to infer and thus successfully predict its pharmacology. This report generated considerable interest in the scientific and lay communities and has spawned a large number of researchers outside of Monell to further investigate its pharmacological properties leading to many publications demonstrating the efficacy of this compound against in vitro models of Alzheimer's disease, cancer, and other diseases of inflammation (a sample of recent publications is at the end of this document).

At Monell, we have continued to pursue our original interest in understanding the mechanism underlying the throat irritation of ibuprofen and, now, oleocanthal. We recently identified the sensory receptor responsible for detecting both of these unrelated compounds, the channel protein, TRPA1. TRPA1 is one of a related series of ion channels that respond not only to chemical stimulation like capsaicin (its receptor is TRPV1) but also to temperature. Further, the localized sensation was explained by the discovery that in the human oral cavity TRPA1 is expressed only in the throat. This is different than TRPV1 which is expressed in both the throat and the mouth, thereby explaining why hot peppers sting the throat and mouth whereas oleocanthal stings only the throat.

Work is continuing at Monell on structure-activity of oleocanthal variants, on the health-benefits of oleocanthal, and on other compounds in EVOO with distinct perceptual and pharmacological properties. We are also deeply interested in understanding what if any relationship exists between TRPA1 activation and anti-inflammatory activity at a mechanistic level. As the role of inflammation in health and disease becomes increasingly apparent, we expect that new findings on this natural anti-inflammatory will have important implications for human health.

Selected health-related publications on oleocanthal: 2011 – 2013

1. ACS Chem Neurosci. 2013 Feb 25. [Epub ahead of print] Olive-Oil-Derived Oleocanthal Enhances β-Amyloid Clearance as a Potential Neuroprotective Mechanism against Alzheimer's Disease: In Vitro and in Vivo Studies. Abuznait AH, Qosa H, Busnena BA, El Sayed KA, Kaddoumi A.

2. Curr Med Chem. 2013 Mar 15. [Epub ahead of print] Oleocanthal inhibits proliferation and MIP-1α expression in human multiple myeloma cells. Scotece M, Gómez R, Conde J, Lopez V, Gómez-Reino JJ, Lago F, Smith AB, Gualillo O.
3. Bioorg Med Chem. 2013 Apr 1;21(7):2117-27. doi: 10.1016/j.bmc.2012.12.050. Epub 2013 Jan 9. Olive secoiridoids and semisynthetic bioisostere analogues for the control of metastatic breast cancer. Busnena BA, Foudah AI, Melancon T, El Sayed KA.
4. J Nutr Biochem. 2013 Mar 7. pii: S0955-2863(12)00309-9. doi: 10.1016/j.jnutbio.2012.12.011. [Epub ahead of print] Effect of olive oil phenols on the production of inflammatory mediators in freshly isolated human monocytes. Rosignoli P, Fuccelli R, Fabiani R, Servili M, Morozzi G.
5. Life Sci. 2012 Dec 10;91(23-24):1229-35. doi: 10.1016/j.lfs.2012.09.012. Epub 2012 Oct 5. Further evidence for the anti-inflammatory activity of oleocanthal: inhibition of MIP-1α and IL-6 in J774 macrophages and in ATDC5 chondrocytes. Scotece M, Gómez R, Conde J, Lopez V, Gómez-Reino JJ, Lago F, Smith AB 3rd, Gualillo
6 J Nat Prod. 2012 Sep 28;75(9):1584-8. Epub 2012 Sep 18. Modulation of tau protein fibrillization by oleocanthal. Monti MC, Margarucci L, Riccio R, Casapullo A.
7 Food Funct. 2011 Jul;2(7):423-8. doi: 10.1039/c1fo10064e. Epub 2011 Jul 7. New insights on the interaction mechanism between tau protein and oleocanthal, an extra-virgin olive-oil bioactive component. Monti MC, Margarucci L, Tosco A, Riccio R, Casapullo A.
8. Carcinogenesis. 2011 Apr;32(4):545-53. doi: 10.1093/carcin/bgr001. Epub 2011 Jan 7. p-HPEA-EDA (Oleocanthal), a phenolic compound of virgin olive oil, activates AMP-activated protein kinase to inhibit carcinogenesis. Khanal P, Oh WK, Yun HJ, Namgoong GM, Ahn SG, Kwon SM, Choi HK, Choi HS.
9. Planta Med. 2011 Jul;77(10):1013-9. doi: 10.1055/s-0030-1270724. Epub 2011 Feb 15. (-)-Oleocanthal as a c-Met inhibitor for the control of metastatic breast and prostate cancers. Elnagar AY, Sylvester PW, El Sayed KA.