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Extra virgin olive oil and ibuprofen share a common receptor, study suggests

Recent research has found that the TRPA1 receptor is shared between oleocanthal in extra virgin olive oil and the non-steroidal anti-inflammatory drug ibuprofen.

It has been found by a team from the Monell Center (PA, USA) and two other institutions that the TRPA1 receptor is activated by two structurally unrelated compounds. One of these is oleocanthal, a natural polyphenolic anti-inflammatory compound found only in virgin olive oil. The other is the non-steroidal anti-inflammatory drug ibuprofen.

> "...oleocanthal inhibits cyclooxygenase enzymes with a similar pharmacological action to that of ibuprofen."

It was also shown by the team of researchers that the TRPA1 receptor is primarily located to the back of the throat. This is where the distinctive irritating sting of olive oil is felt. This unique sensation and the accompanying 'cough' are regarded among connoisseurs as indicators of high-quality olive oil. "We believe that the TRPA1 receptor elicits cough to protect the lungs from chemical insult, for example from toxins in the air," said Paul Breslin (Monell Center), one of the authors of the article.

In 2005, Monell researchers and collaborators announced the discovery that oleocanthal inhibits cyclooxygenase enzymes with a similar pharmacological action to that of ibuprofen. These findings were based on the observation that olive oil irritates the back of the throat in the same way as that experienced when ingesting liquid ibuprofen. It was also confirmed by the scientists that the irritating throat sting associated with extra virgin olive oils was caused by oleocanthal.

The latest study, published in the *Journal of Neuroscience*, expands on previous findings by isolating TRPA1 as the receptor that is activated by both oleocanthal and ibuprofen. These latest results identify the activation of TRPA1 by both agents as the cause of the distinctive irritation experienced with oleocanthal and ibuprofen.

It is hoped that these latest results will provide novel insights into anti-inflammatory pharmacology. "This receptor may be used to identify other anti-inflammatory compounds that, like ibuprofen and oleocanthal, help prevent major lethal disease," said Breslin. "Additionally, since we know how to inhibit this receptor, it may be possible to develop liquid anti-inflammatory medicines that are less aversive. This would especially benefit children, who are unable to swallow pills."

The combination of sensory, chemical and molecular methods used in this study may offer insight into other aspects of inflammation and disease. "Oleocanthal and ibuprofen are chemically unrelated, yet both are potent anti-inflammatory compounds that activate the TRPA1 receptor and cause sensory irritation," said Gary Beauchamp (Monell Center) who also worked on the study.

> "The combination of sensory, chemical and molecular methods used in this study may offer insight into other aspects of inflammation and disease."

It is hoped that future work will explore several contradictory relationships that exist between the health-promoting aspects of oleocanthal and ibuprofen. "An understanding of this connection could someday lead to identification of new anti-inflammatory pathways," said Beachamp.

Sources: Smith AB 3rd, Beauchamp GK, Breslin PA *et al.* Unusual pungency from extra-virgin olive oil is attributable to restricted spatial expression of the receptor of oleocanthal. *J. Neurosci.* 31(3), 999–1009 (2011); NSAID receptor responsible for olive oil's 'cough' and more: www.monell.org/news/news_releases/trpa1_receptor

About the News in Brief

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New CDC guidelines on HIV pre-exposure prophylaxis

Following recent positive trial results, the US CDC recommends tenofovir for HIV pre-exposure prophylaxis in high-risk men who have sex with men.

Pre-exposure prophylaxis (PrEP) for HIV is an idea that has been considered for some time. Concerns have been raised regarding cost–effectiveness, target populations and the development of drug-resistant HIV strains, but recent guidance from the US CDC has come out in favor of this method for controlling the spread of HIV in high-risk populations, specifically men who have sex with men (MSM). Noting that an effective vaccine is 'years away', a recent report stated "mounting evidence that antiretroviral drugs may be able to play an important role in reducing the risk of HIV infection."

The drugs concerned are tenofovir and emtricitabine in combination, or tenofovir alone, which have been examined in PrEP trials taking place in a variety of locations worldwide. At this stage, no major safety problems have arisen, and the indications are that this therapy is safe and effective in reducing HIV infection.

At present the recommendations only indicate PrEP for MSM who do not consistently use other methods to control HIV transmission (i.e., condoms), and who experience "frequent partner change or concurrent partners in a geographic setting with high HIV prevalence," acknowledging the potential for effects and the high cost of the medication. Given the often-low adherence to medication observed in the trial that led to these guidelines being issued, adherence counseling was encouraged, along with a specific warning against "intermittent" dosing just before and/or after sex.

Although concerns and queries such as those mentioned previously are acknowledged in the CDC report, its timing – very shortly after the first results of a related trial – may indicate an overall policy shift towards PrEP. Citing its use in such situations as the prevention of HIV transmission from mother to newborn during delivery, and in healthcare workers with accidental exposure, CDC information released seem to signal its support for the eventual use of PrEP in a broader range of high-risk populations other than MSM.

Correctly handled, it appears that PrEP does have the potential to have a great impact on the current HIV situation worldwide. One of the most important aspects of this form of HIV prevention – oral self-administration of antiretroviral drugs – is that it is fully under the control of the individual concerned, a significant factor in its favor. While condom usage is an effective method of infection prevention when used, it is not female-controlled and it is not always possible for women to insist on this method, which can lead to unwanted exposure risk. PrEP, on the other hand, is a potentially female-controlled infection prevention method, something that could change the course of the HIV epidemic.

Sources: Smith DK, Grant RM, Weidle PJ *et al.* Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *Morb. Mortal. Wkly Rep.* 60(3), 65–68 (2011); CDC trials of pre-exposure prophylaxis for HIV prevention fact sheet: www.cdc.gov/hiv/prep/resources/factsheets/index.htm

Antibiotic may have potential uses in the development of new anticancer drugs, study suggests

It has been found by a team of researchers from the Indiana University School of Medicine (IN, USA) that an antibiotic that has immunosuppressive properties could be used to develop new anticancer agents. The findings of this recent study have been published in *Chemistry and Biology*.

The study found that the compound tautomycetin targets an enzyme called SHP2, which is known to have a significant role in cell activities including proliferation and differentiation. It has been previously been found that SHP2 mutations can cause several types of leukemia and solid tumors.

The team of researchers noted the possibility of developing anticancer agents after they studied the mechanisms by which tautomycetin exerts its immune suppression activities. The recent findings give a call for optimism as SHP2 is a member of the protein tyrosine phosphotases (PTPs) family of enzymes, which play a pivotal role in the signaling processes that control all vital cellular functions. Inhibition of PTP activity has been associated with several diseases, such as cancer, diabetes and various immune system impairments. To date it has been difficult to develop drugs that specifically target PTPs owing to their make up.

One of the lead authors of the paper, Zhong-Yin Zhang (Indiana University School of Medicine) said: "So we have identified a lead – a natural product produced by the bacteria *Streptomyces* – that should serve as a foundation for the development of therapeutic agents for a large family of protein tyrosine phosphotase targets. Until now, these targets, including SHP2 for leukemia and other cancers, have been deemed undruggable."

Sources: Liu S, Yu Z, Yu X *et al.* SHP2 is a target of the immunosuppressant tautomycetin. *Chem. Biol.* 18(1), 101–110 (2011); Antibiotic offers potential for anti-cancer activity: http://communications.medicine.iu.edu/newsroom/stories/2011/antibiotic-offers-potential-for-anti-cancer-activity/

An experimental morphine-like drug appears more potent and longer lasting than standard morphine

A novel drug, morphine-6-0-sulfate, has been reported by Joseph Holtman Jr *et al.* as potentially being more potent and longer-lasting than morphine in the treatment of pain in rats. The research was carried out by Holtman at the University of Kentucky's College of Medicine (KY, USA). Holtman has since moved to Loyola University (IL, USA).

Morphine, oxycodone and hydrocodone are μ-opiods that bind to specific opiod receptors in the central and peripheral nervous systems and are considered the primary drugs for treating acute, chronic and cancer-related pain in patients. The potential pain-relieving drug morphine-6-0-sulfate is a derivative on the μ-opiod morphine.

Holtman *et al.* treated rats with both morphine and morphine-6-0-sulphate by mouth, intravenously and via injection into the space surrounding the spinal cord. Various tests were carried out to assess the rat's sensitivity to pain, including shining a warm light beam onto their tail to test nociceptive pain. The time it took for them to flick their tails away was then recorded. It was discovered that morphine-6-0-sulphate was ten-times more potent than typical morphine when administered into the space surrounding the spinal cord, five-times more potent intravenously and twice as potent when taken by mouth. Furthermore, morphine-6-0-sulphate maintained its greatest effects for twice as long as morphine, lasting for 3 h.

Holtman *et al.* also found morphine-6-0-sulfate to be more potent in neuropathic and inflammatory pain, where morphine is not typically as effective. The neuropathic test was carried out using chronic constriction nerve injury and allodynia and the inflammatory pain was created via a formalin test.

There are many effects associated with morphine, including constipation, nausea, vomiting and drowsiness. Constipation can result in extended hospital stays as consultants are not able to discharge surgery patients until they have had a bowel movement. It can also prevent patients from taking the prescribed morphine for pain management as it can make them extremely uncomfortable. Promising results from Holtman's study suggest that whilst morphine-6-0-sulfate can cause constipation, this is only at doses 10–20-times higher than the effective dose for pain management.

Another major problem with morphine is the ability of the patient to build up tolerance to the drug; this occurred within 10 days in the rats. However, it took 25 days for tolerance to build up to morphine-6-0-sulphate. These results show great potential and has led Holtman *et al.* to describe the novel drug morphine-6-0-sulphate as potentially being "an interesting drug for further study".

The funding company InSys Therapeutics, Inc. now has a license to potentially develop the drug for use in humans.

Source: Holtman HR Jr, Crooks PA, Johnson-Hardy J, Wala EP. Antinociceptive effects and toxicity of morphine-6-O-sulfate sodium salt in rat models of pain. *Eur. J. Pharmacol.* 648 (1–3), 87 (2010).

Antidepressants could reduce hot flashes in menopause

Researchers at the University of Pennsylvania School of Medicine (PA, USA) have revealed that the frequency and severity of hot flashes could be reduced in women who are in either the transition to menopause or are postmenopausal, by administration of the antidepressant escitalopram.

Menopausal hot flashes are a symptom of menopause but do not affect all women. Hot flashes are characterized by a spreading feeling of warmth, which can be anywhere on the body but is often concentrated in the head and neck. Flashes are a symptom of the changing hormone levels that occur during menopause.

Scientists evaluated the efficacy of escitalopram versus a placebo to reduce the frequency and severity of hot flashes in healthy women. The important modifiers of race, menopausal status, depressed mood and anxiety were also examined.

The randomized trial was a multicenter study including 205 women, a number of racial groups were evaluated. The women were prescribed 10–20 mg per day of escitalopram or a matching placebo for a period of 8 weeks. The frequency and severity of the flashes was assessed by prospective daily diaries at weeks 4 and 8.

The study indicated that escitalopram was associated with a significant reduction in the frequency of hot flashes in comparison with the placebo. The results were adjusted for race, site of heat and baseline frequency of hot flashes. The hot flash frequency at week 8 was found to have reduced by 47% for those women receiving escitalopram, whereas the group receiving the placebo experienced a 33% reduction in hot flash frequency.

Although the decrease in hot flash frequency and severity may appear modest, the participants of the study indicated that these improvements were meaningful, this was indicated by their satisfaction and wish to continue receiving treatment. Ellen Freeman, the lead researcher of the study, comments "our findings suggest that among healthy women, 10–20 mg/day of escitalopram provides a nonhormonal, off-label option that is effective and well tolerated in the management of menopausal hot flashes."

The group suggests further research is required to investigate the efficacy of selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors compared with hormonal therapy in the treatment of hot flashes in menopausal women.

Source: Freeman EW, Guthrie KA, Caan B *et al.* Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA* 305(3), 267–274 (2011).