How Artificial Sweeteners Reduce Diabetes-Associated Blood Vessel Injury in the Eye

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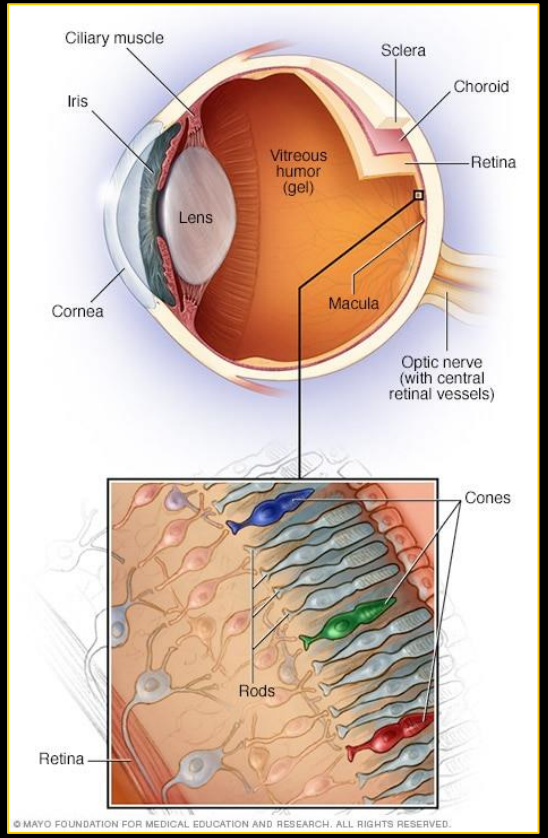
BARS conference, 27 September 2019, 11:50-12:15

Crown Plaza Hotel, Liverpool

@DrHaviChichger

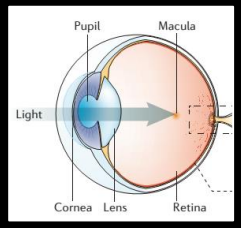
Diabetic Eye Disease



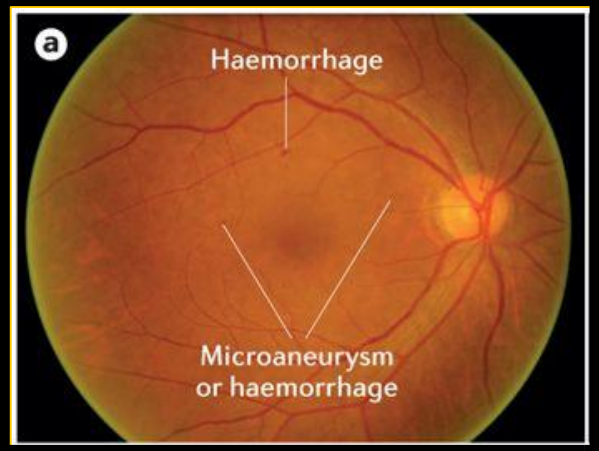
- Diabetes – 4.5 million UK, ~10% global community
- Diabetic eye disease comprises a group of eye conditions including diabetic retinopathy (DR), diabetic macular edema (DME), cataract, and glaucoma.
- All forms of diabetic eye disease have the potential to cause severe vision impairment, vision loss and blindness.
- In 2014, 54.6% patients with type I diabetes had DR; and 30% patients with type II diabetes had DR

Mathur R et al, 2017, RNIB; Diabetes UK 2018; Eschenbach Optik 2019; Mayo Clinic 2019

Clinical signs of diabetic retinopathy on fundoscopic examination

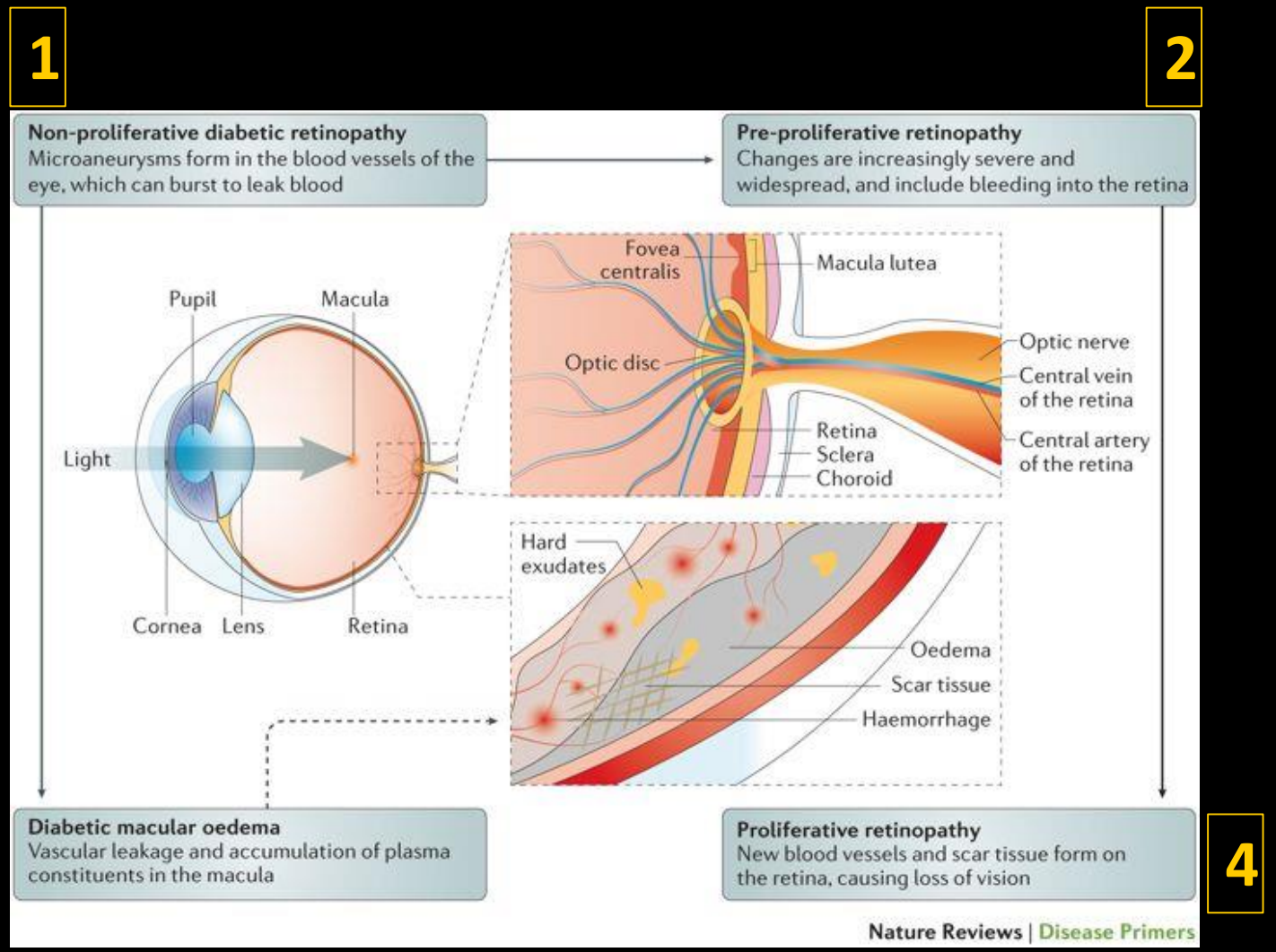


Mild, non-proliferative DR



Wong TY, 2016, Nature Reviews Disease Primers

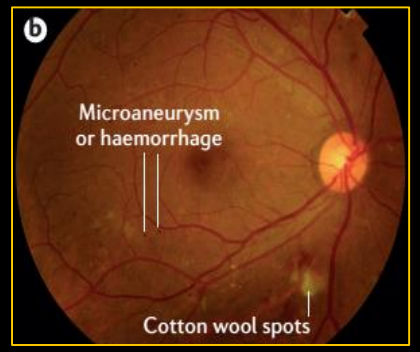
Pathogenic events in DR



Wong TY, 2016, Nature Reviews Disease Primers

Macular oedema (fluid leak)

Proliferative retinopathy (new blood vessel formation)

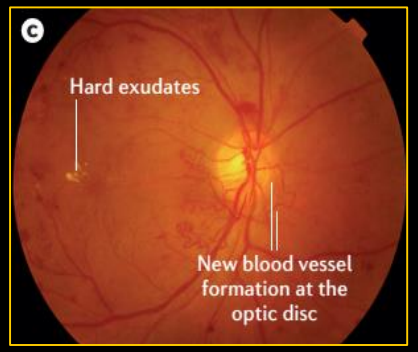


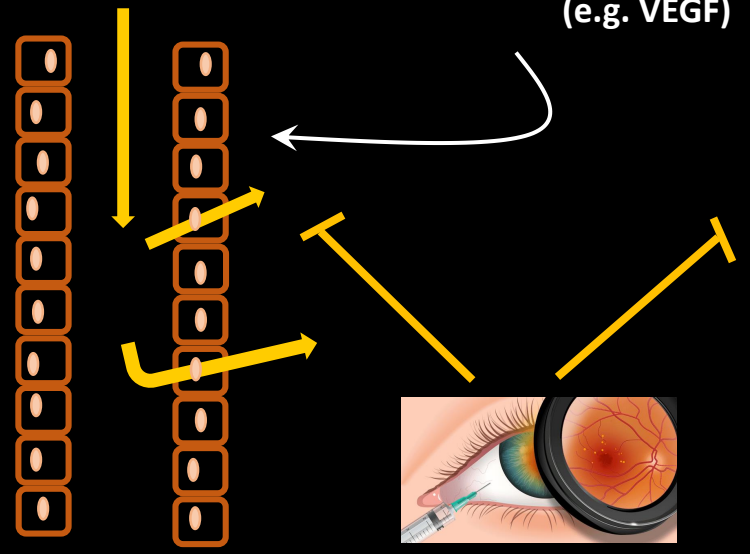
Diabetes

High blood glucose

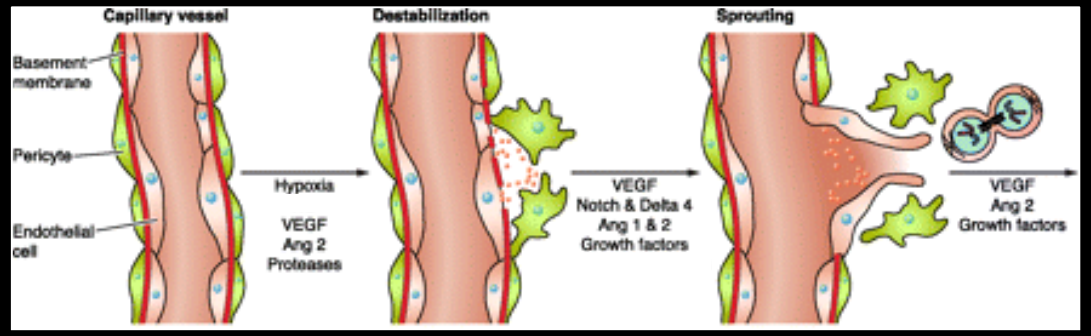
Physiological stress

Release of factors (e.g. VEGF)





- Afilbercept (Eylea)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Pegaptanib (Macugen)



Breakdown of junctions between cells

Cells divide

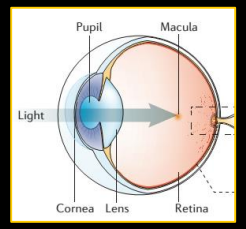
Cells move

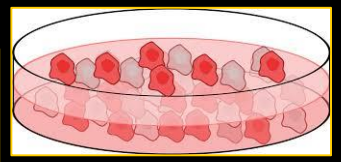
Cells become sticky

Cells form tubes

Clapp C, 2009, Physiological Reviews

Methods to study DR processes in the lab

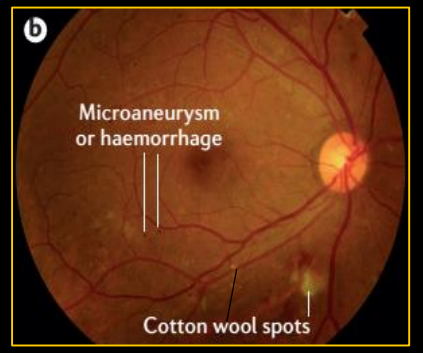




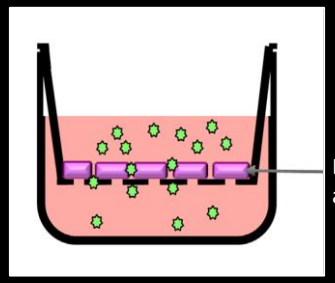
Retinal microvascular endothelial cells

+ VEGF

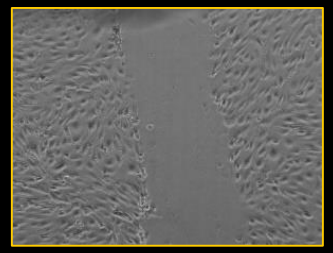
Moderate



Fluid leak

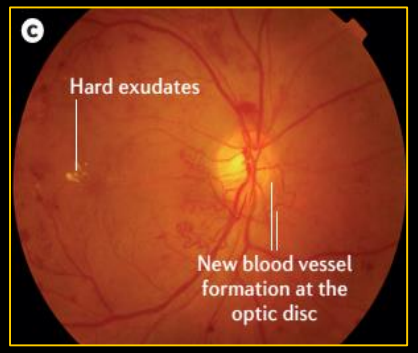


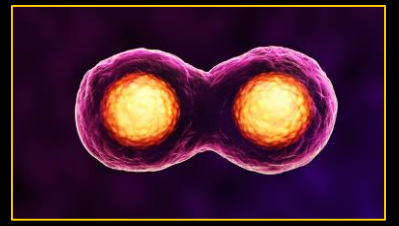
Fluorescent dextran

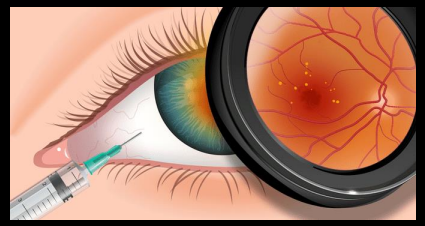


+ VEGF

Proliferative



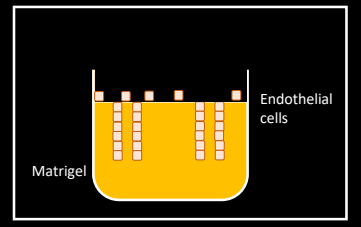


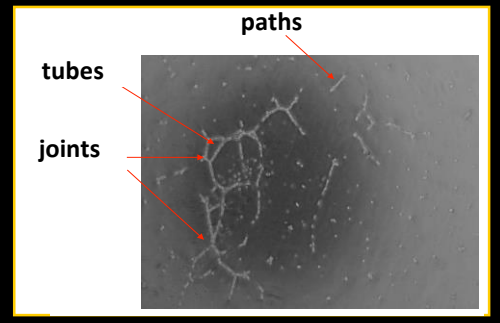


Cell migration

Tube formation

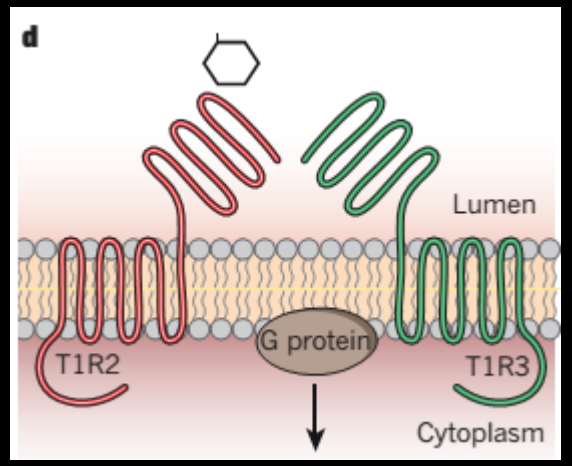
Cell proliferation





Chichger H, 2015, FASEB, 2016, AJRCMB

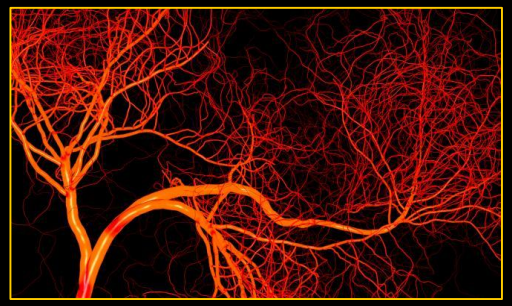
Lessons from the lung – the sweet taste receptor

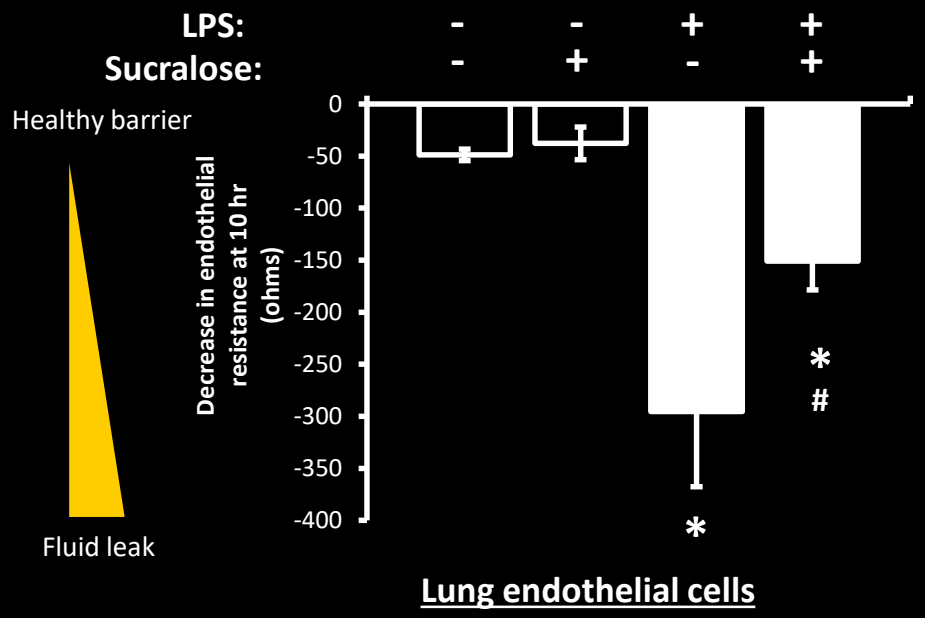


Ca^{2+}

IP_3

PKC



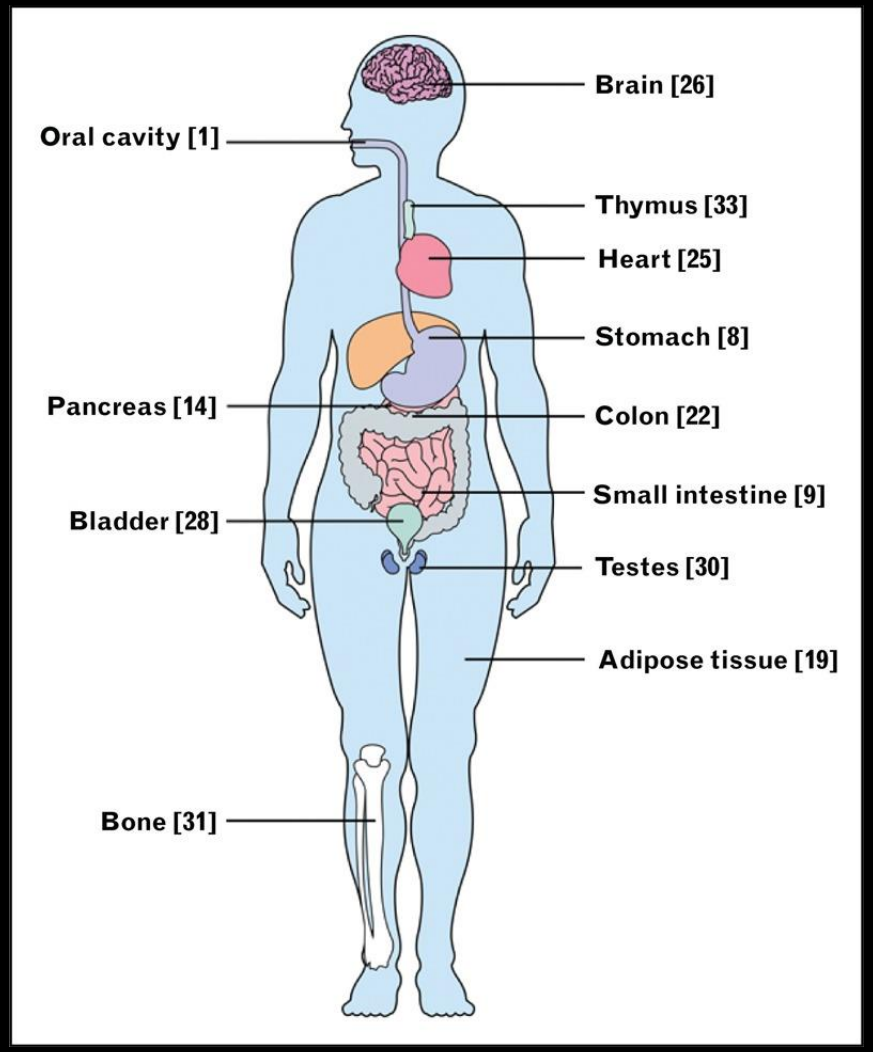


IP3, inositol triphosphate; **PKC,** protein kinase C**; LPS.** Lipopolysaccharide**,** *p<0.05 vs LPS vehicle**,** #p<0.05 vs Suc vehicle

Harrington EO & Chichger H, 2017, AJP Lung

Sweet taste receptor

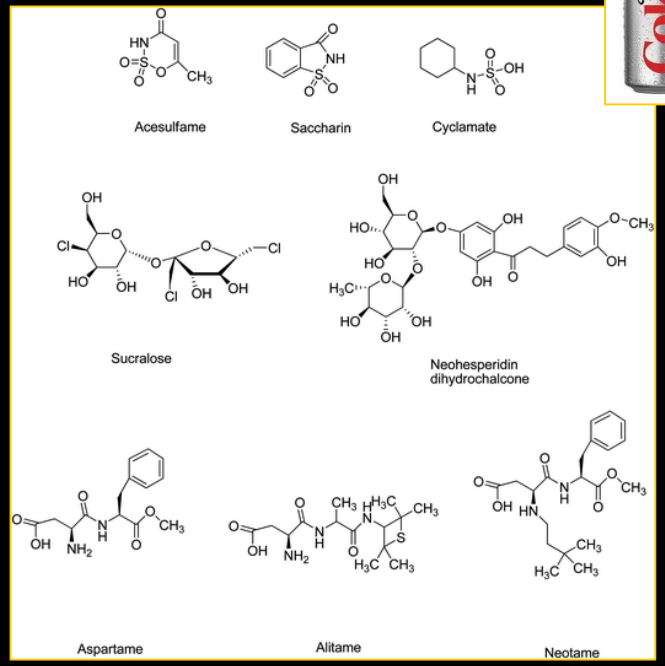
- Receptor which has remained unchanged through evolution - important
- Oral and extra-oral localisation
- Activated by high concentration glucose or low concentration of acutely-sweet artificial sweeteners



Behrens, *Physiol Behav,* 2011; Hass, *Cell Tissue Res,* 2010; Dyer J, *Biochem Soc Trans;* 2005; Henquin, *Sci Signal,* 2012; Masubuchi, *PloS One,* 2013; Rozengurt, *AJP Gastro,* 2006; Ren, *Front Integr Neurosci,* 2009; Foster, *Plos One,* 2013; Elliott, *J Urol,* 2011; Mosinger, *PNAS,* 2013; Simon, *PloS One,* 2014; Max, *Nat Genet,* 2001

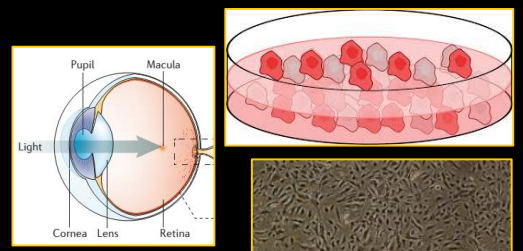
Sweet taste molecules

Commercial name	Sweet molecule	Sweet taste perception relative to table sugar
Equal	Cyclamate	30-50
Equal	Aspartame	160-200
Sunett	Acesulfame K	200
Sweet n Low	Saccharin	300-450
Splenda	Sucralose	600
NHDC	Neohesperidin	1500 - 1800
Aclame	Alitame	2000
E961	Neotame	7000-8000



Natural sweet molecule	Sweet taste perception relative to table sugar
Mabinlin	400
Pentadin	500
Brazzein	500
Monelin	800-1000
Thaumatin	3000

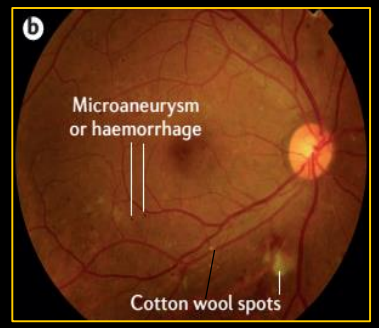
Does the sweet taste receptor play a role in fluid leak and new vessel formation in the retina?



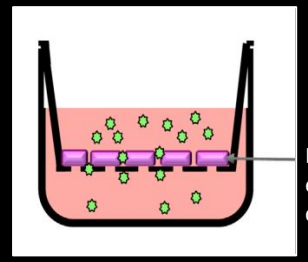
Retinal microvascular endothelial cells

+ VEGF

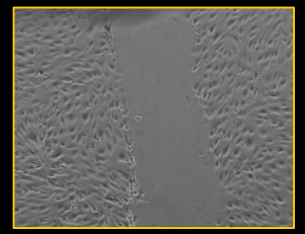
Moderate



Fluid leak

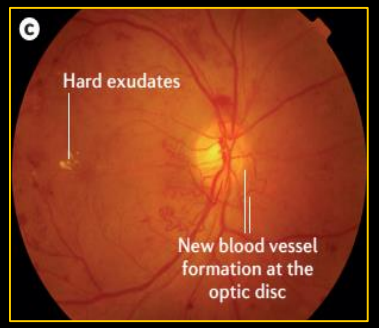


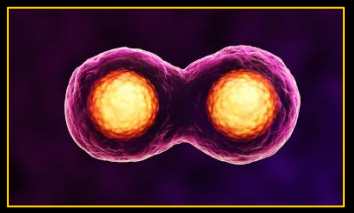
Fluorescent dextran

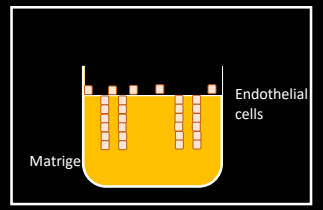


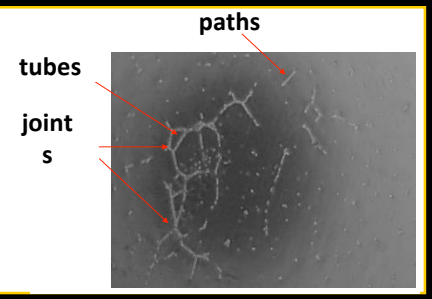
+ VEGF

Proliferative





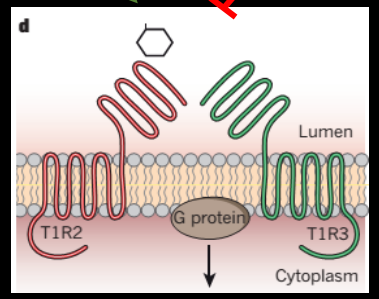




Cell migration
Tube formation
Cell proliferation

+ Artificial sweeteners

+ lactisole

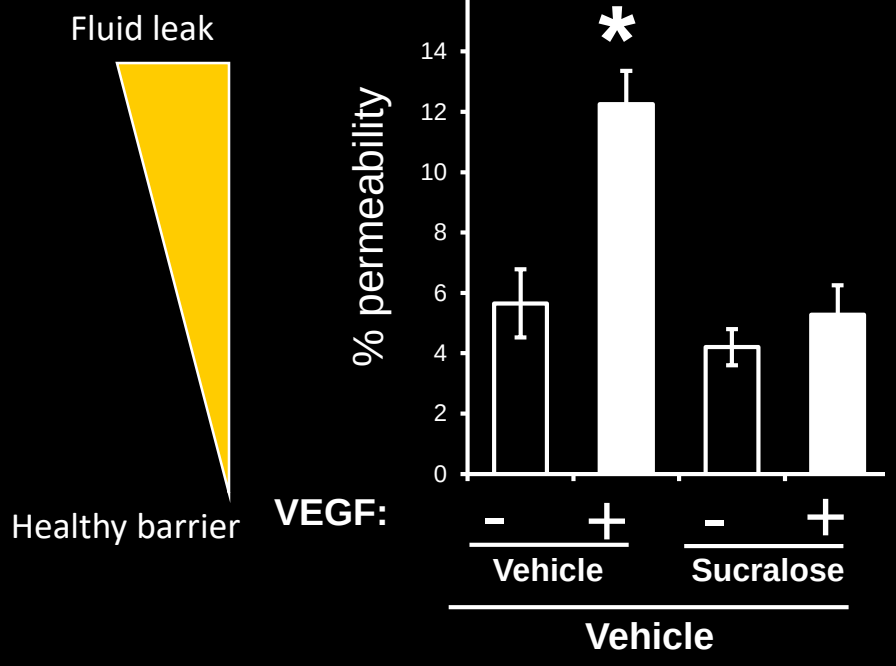


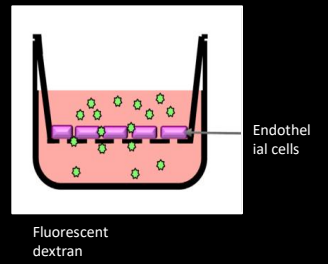
Saccharin (0.1 µM); Sucralose (0.1 µM)

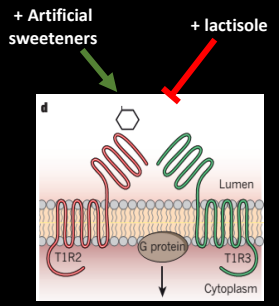
VEGF – vascular endothelial growth factor

Chichger H, 2015, FASEB, 2016, AJRCMB

Sucralose reduces VEGF-induced leak
- dependent on sweet taste receptor



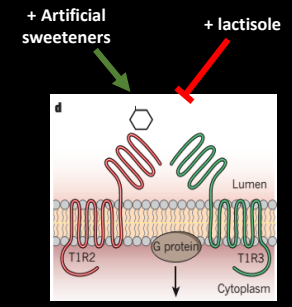


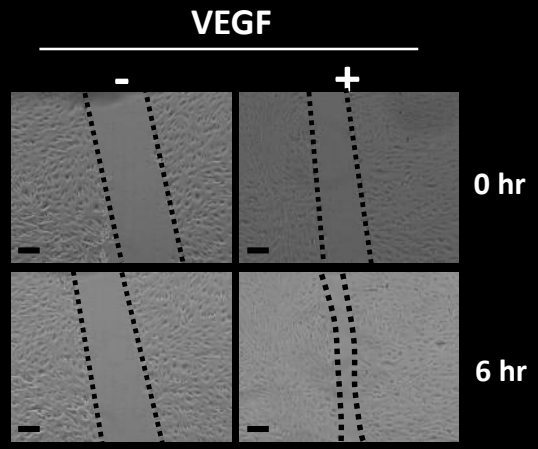


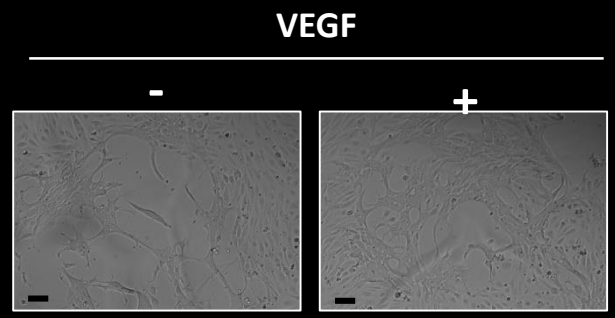
*p<0.05 vs vehicle for VEGF; n = 6

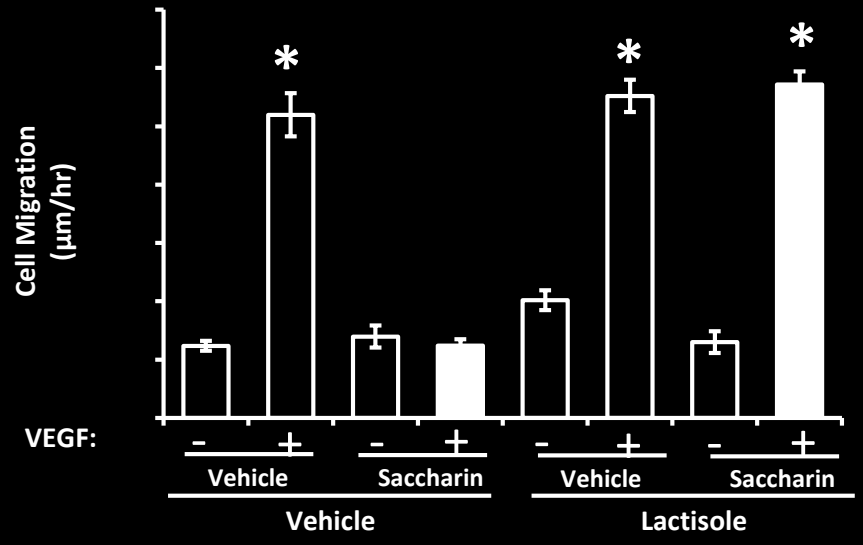
Lizunkova P, 2019, Graefe's Clinical and Experimental Ophthalmology

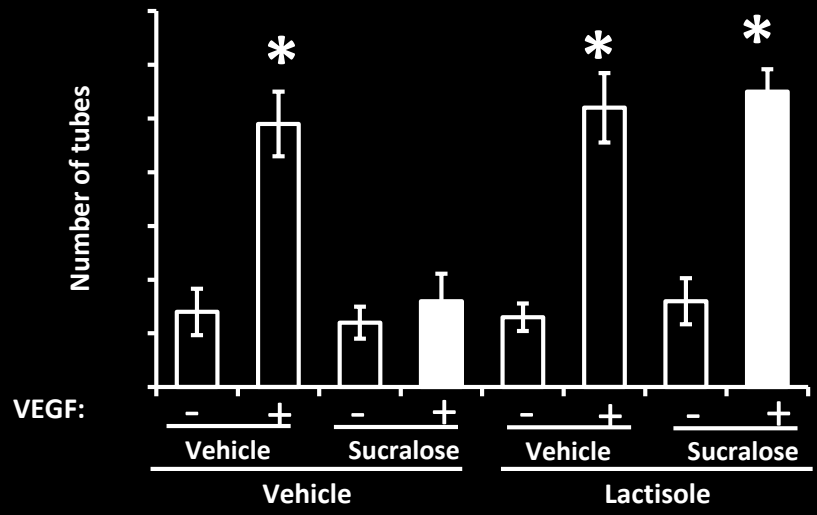
Artificial sweeteners reduce angiogenesis











*p<0.05 vs vehicle for VEGF; n = 4-6. x 10 magnification, scale bar 20 µm *Lizunkova P, 2019,* Graefe's Clinical and Experimental Ophthalmology

Diabetes

VEGF

Artificial sweeteners

T1R3

VEGFR2

Src

RhoA

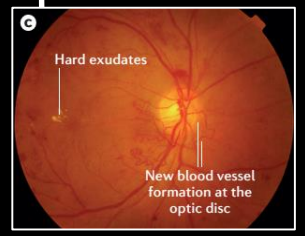
Akt

Migration

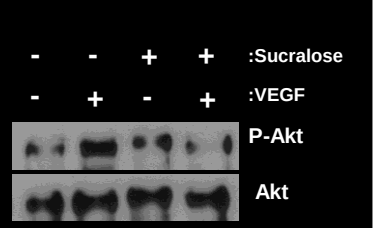
Adhesion

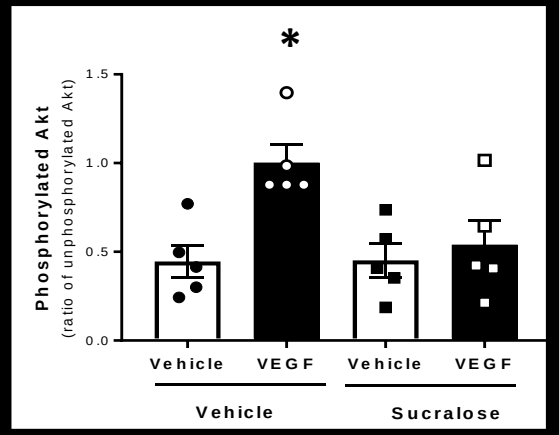
Proliferation

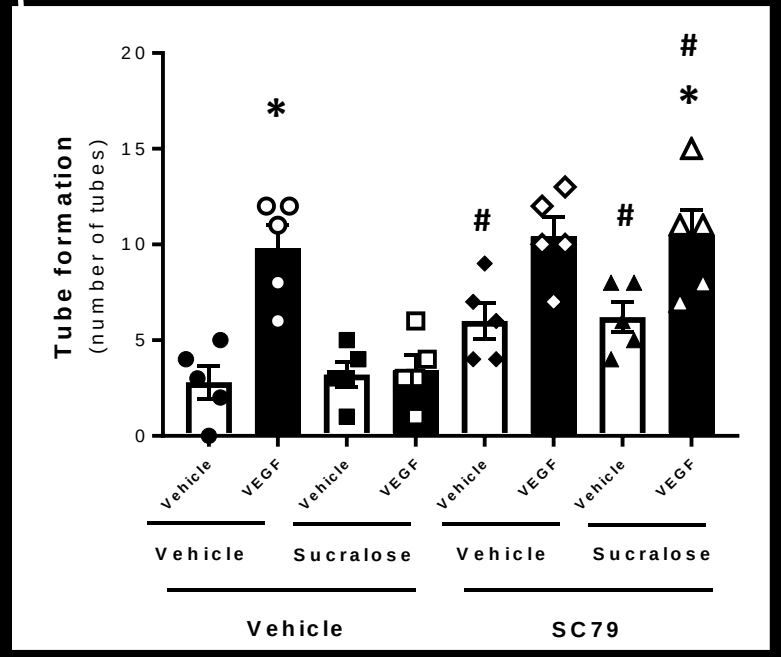
Tube formation



Proliferative (tube formation)



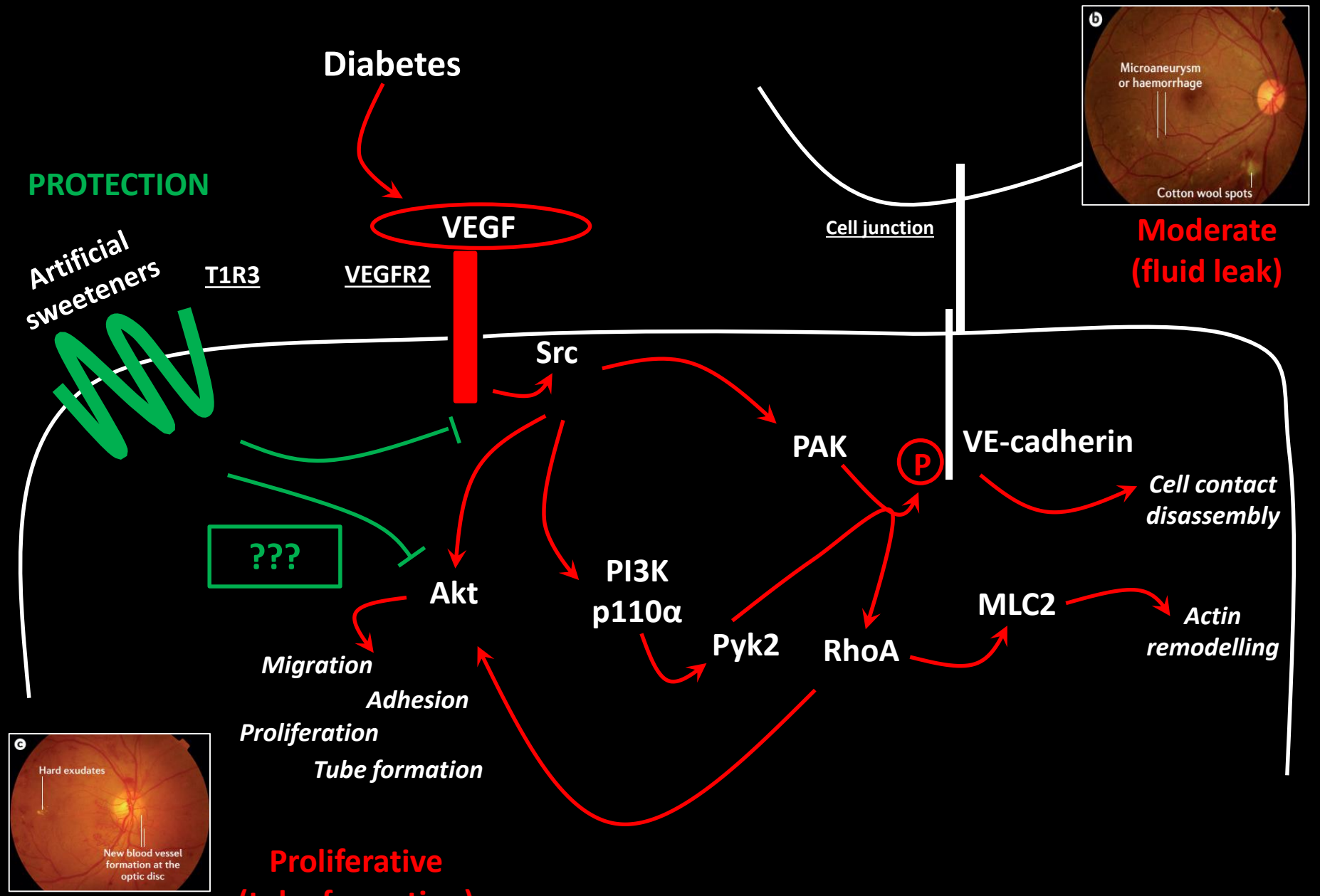




Mean ± SD, *p<0.05 vs vehicle for VEGF

SC79 – Akt activator; Akt – protein kinase B; Src – kinase; VEGFR2 – VEGF receptor

Lizunkova P, 2019, Graefe's Clinical and Experimental Ophthalmology


Diabetes
PROTECTION
VEGF
Artificial sweeteners
T1R3
VEGFR2
Cell junction
Microaneurysm or haemorrhage
Cotton wool spots
Moderate (fluid leak)
Src
PAK
P
VE-cadherin
Cell contact disassembly
???
Akt
PI3K p110α
Pyk2
RhoA
MLC2
Actin remodelling
Migration
Adhesion
Proliferation
Tube formation
Hard exudates
New blood vessel formation at the optic disc
Proliferative (tube formation)

The controversy

If people with diabetes eat more Splenda, will it stop their proliferative retinopathy getting worse?

Newsbeat

Fizzy and diet drinks: What we know and what we don't

By Christian Hewgill
Newsbeat reporter

4 September 2019 Share

Diet debate: Are diet drinks a no-go?

By James Gallagher
Health editor, BBC News website

4 January 2017 | Health Share

It's rare in life to have your cake and eat it. But are low-calorie sweeteners the guilt-free way to be naughty?

Soft drinks, including sugar-free, linked to increased risk of early death

Drink more water, say experts as they argue study proves need for curbs on consumption

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2*], David Zeevi[2*], Gili Zilberman-Schapira[1*], Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

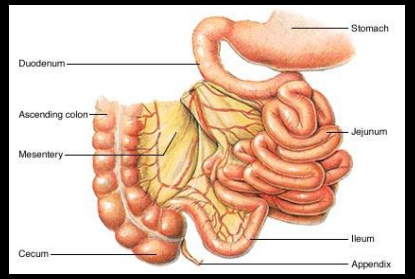
Artificial Sweeteners: The Culprit to Weight Gain and Diseases, Study Says

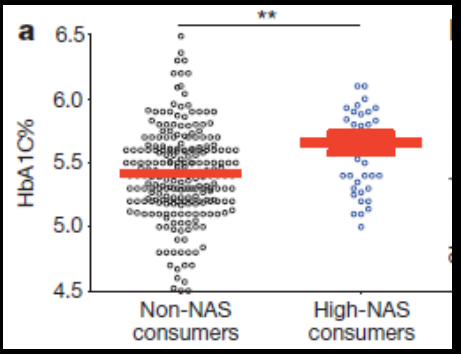
Pepsi to drop artificial sweetener aspartame

By Michelle Roberts
Health editor, BBC News online

27 April 2015 | Health Share

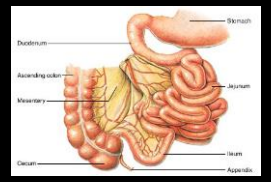
A controversial artificial sweetener is being removed from Diet Pepsi in the US amid consumer concerns about its safety.

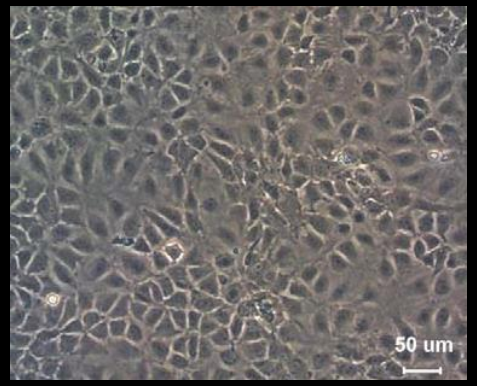


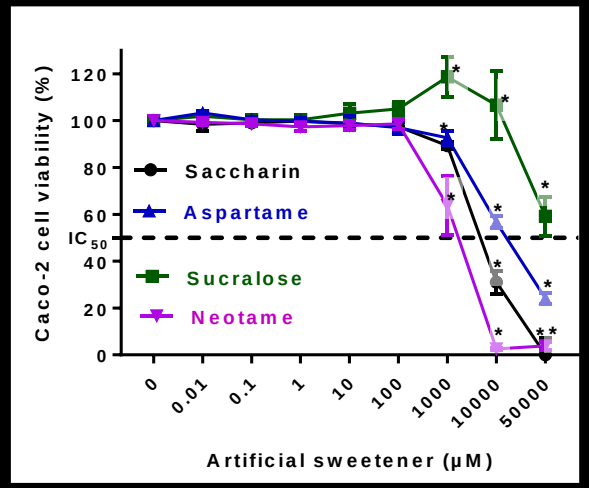


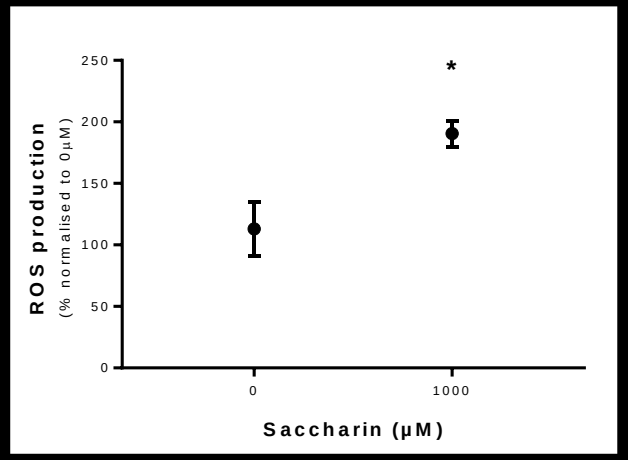
Suez, *Nature*, 2014

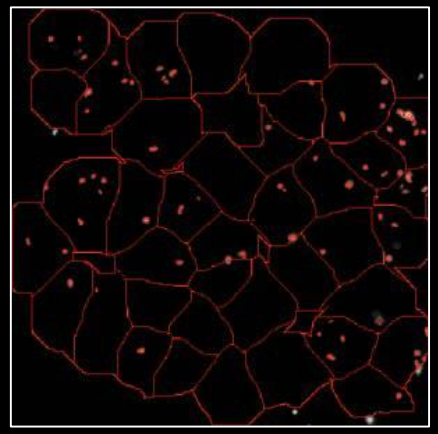
Artificial sweeteners in the diet – negative consequences

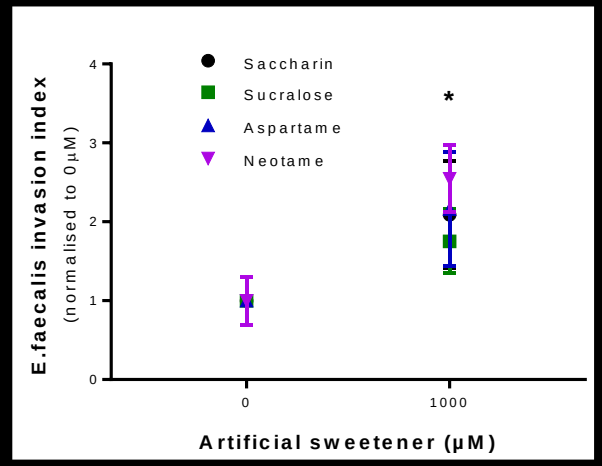












Mean ± SEM, *p<0.05 vs 0 µM Invasion index = CFU/Caco2 cell #

Steinberg, *AJP Cell,* 2006

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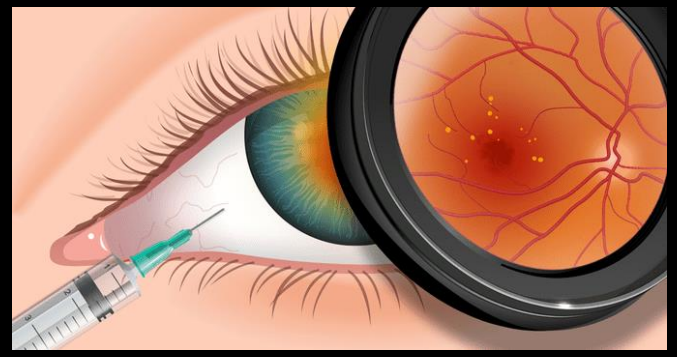

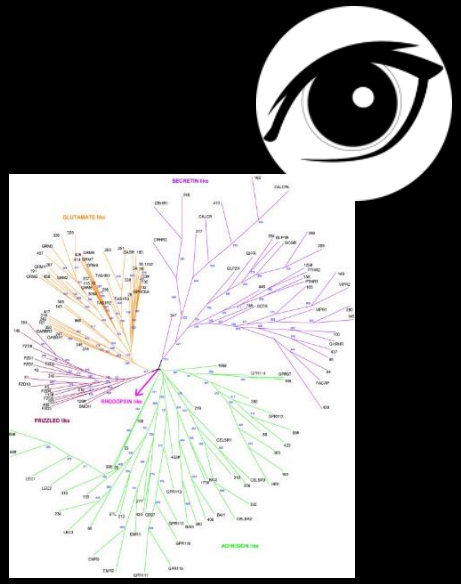

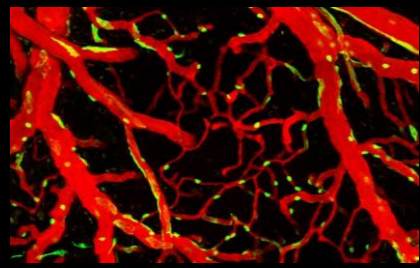

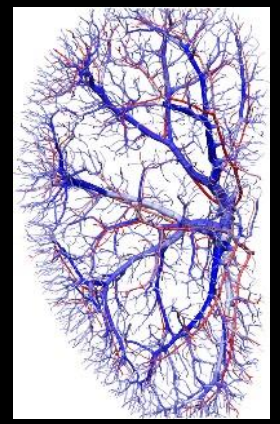

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- Signe Pedersen
- Ana Couto

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