



2018

VIENNA, AUSTRIA

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

SAVE THE DATE : 28-30 JUNE 2018

MASCC/ISOO

ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER



www.mascc.org/meeting



#MASCC18

Cannabis: taste and flavor

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I no related disclosures



Taste Change in Cancer Survivors

Flavor: taste, smell, texture, temperature, vision

Causes of Taste Change in Cancer Survivors:

- Cancer Therapy:
 - Surgery
 - Radiation
 - Chemotherapy
 - Targeted therapies
 - Immunotherapy
- Supportive care/ analgesics/other medications
- Comorbidities
- Oral conditions



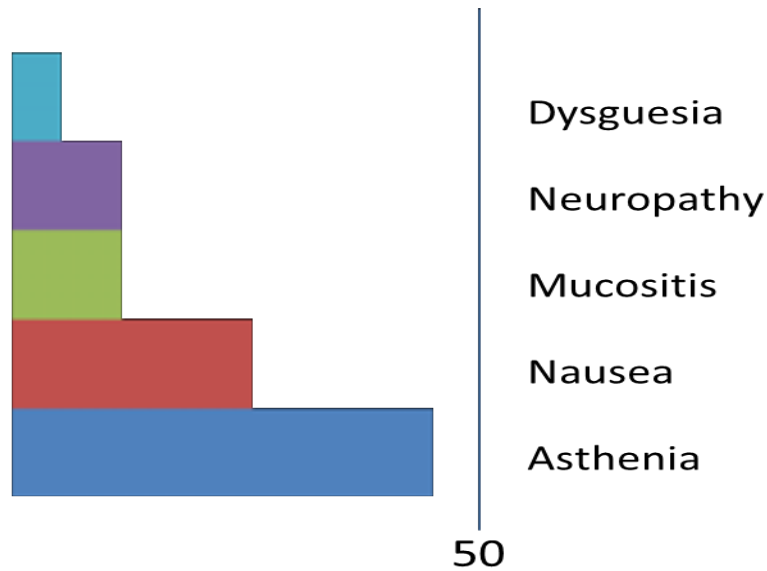


My neighbor came back from a party last night. I'm guessing he couldn't find the toothpaste...



Doctors v Patient Symptom Report in BC Chemotherapy

Physician evaluation (CTCAE)



Patient Report

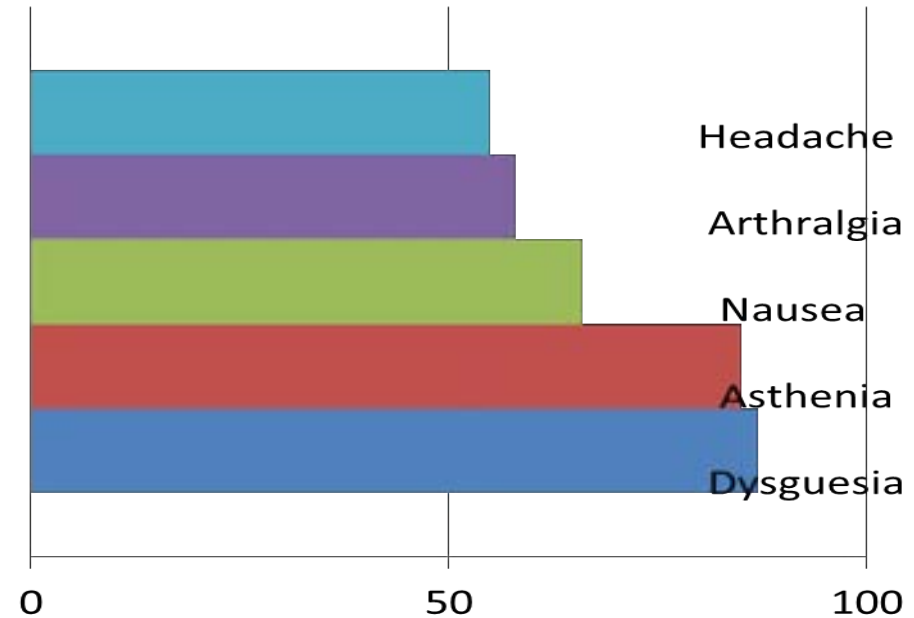
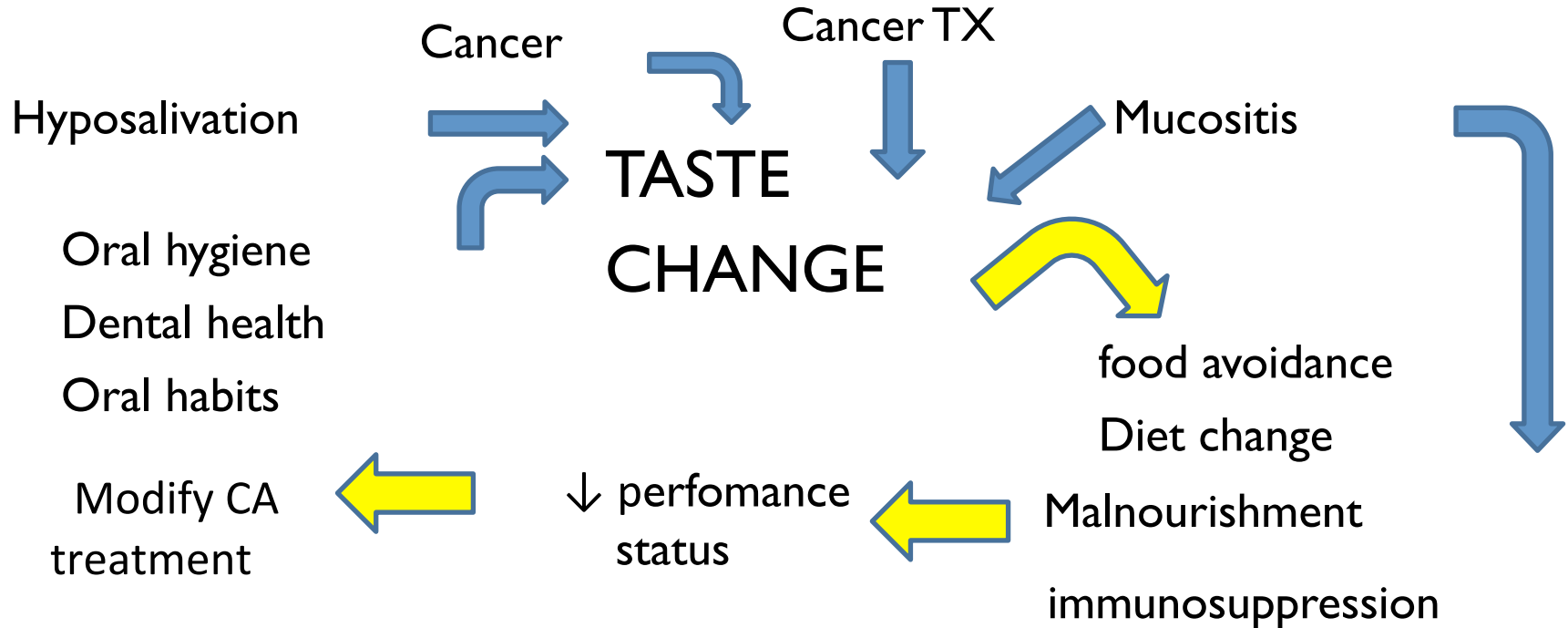


Table 2. Summary of Paired Patient and Physician Questionnaires After Cycle 1*

Item ^b	Questionnaire, No. (%)		Differences Between Patient and Physician (95%CI) ^c
	Patient	Physician	
Nausea (539)			
Incidence	360 (67)	216 (40)	27 (22-31)
Mean grade	1.10	0.59	0.51 (0.43-0.59)
Vomiting (572)			
Incidence	128 (22)	62 (11)	11 (9-14)
Mean grade	0.31	0.16	0.15 (0.11-0.20)
Constipation (546)			
Incidence	268 (49)	65 (12)	37 (33-41)
Mean grade	0.64	0.15	0.49 (0.42-0.54)
Anorexia (563)			
Incidence	297 (53)	41 (7)	46 (41-50)
Mean grade	0.69	0.09	0.60 (0.53-0.66)
Dysgeusia (556)			
Incidence	277 (50)	46 (8)	42 (37-46)
Mean grade	0.61	0.10	0.51 (0.45-0.57)
Diarrhea (567)			
Incidence	81 (14)	25 (4)	10 (7-13)
Mean grade	0.17	0.06	0.11 (0.07-0.14)
Fatigue (532)			
Incidence	400 (75)	132 (25)	50 (46-55)
Mean grade	1.11	0.35	0.76 (0.71-0.79)

Burden of Taste and Smell changes



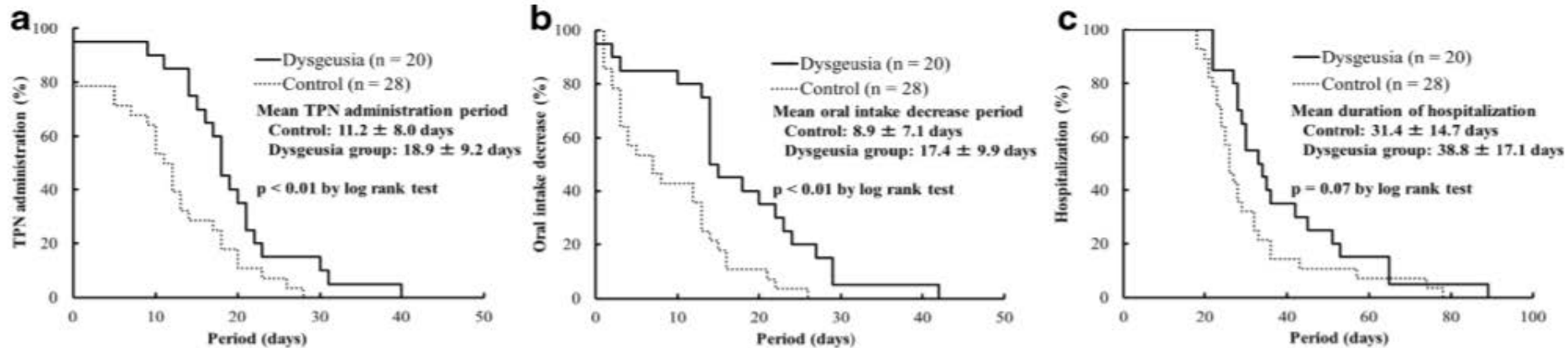
CHEMOTHERAPY-INDUCED TASTE & SMELL Changes

- Limited studies (!)
- Most data in breast cancer (taste changes, metallic dysgeusia, preference for sweet)
- ↑ incidence with docetaxel (possible symptom cluster with CIPN?)
- Impact on fatigue and quality of life!
- Persistence of the symptom after treatment

TASTE AND SMELL AFTER HSCT

Support Care Cancer (2016) 24:3979–3985

3983



Okada N, et al. Sup Care Cancer 2016;24:3979-85

TARGETED THERAPY: TASTE AND SMELL Changes

- Variable incidence:
 - imatinib 13-40%
 - sorafenib 15-30%
 - sunitinib 10-60%
 - everolimus/temsirolimus 10-20%
 - lapatinib 10%
 - vismodegib 50-70%

Taste function following HNC: qualitative research

- “Eating is more than nutrition...it’s also a very pleasurable experience.... my daughters are both, I guess you would call “foodies” ...it is like an activity for us more than just eating food for nutrition, it’s something that we do for fun. We enjoy eating good foods.” (GS=1.54)
- “Having gone through a couple of months of only drinking liquids... it means a lot. I like to eat.” (GS=0.15)
- “Before cancer I ate to live, and now I live to eat...I never really appreciated food in the way that I do now that I can eat again. It’s a gift I appreciate a lot more.” (GS=0.21)
- “The taste of food is of significant importance...it’s almost up there with sex in terms of you know, what it brings from a list of things you couldn’t live without...” (GS=0.02)

Taste

Evaluate content of food & prevent ingestion of toxic substances

- Bitter: detects submicromolar levels of toxic/noxious compounds
- Sour: warns of noxious/poisonous agents
- Sweet: identifies energy-rich nutrients
- Salt: ensures intake for electrolyte balance
- Umami: (savory/pleasure)
 - recognizes amino acids (glutamate, aspartate); MSG

Gustation

Specialised epithelial cells:

Tongue

Soft palate

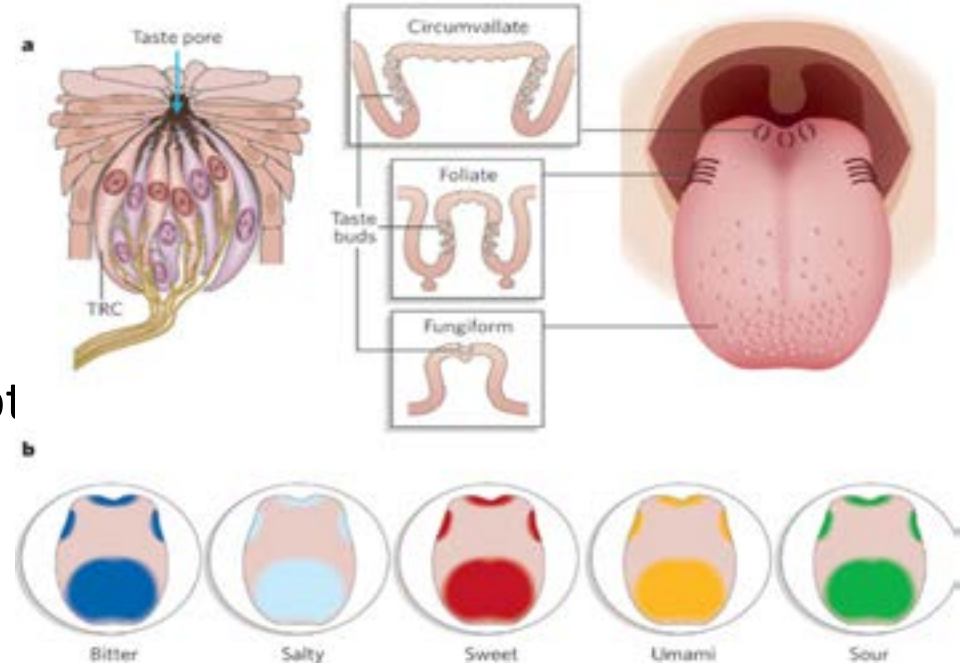
Pharynx

Larynx

Upper 1/3 of oesophagus

Each taste bud: 50-100 taste-receptor cells; lifespan of ~10-14 days

No segregation of taste qualities in human tongue



Scott, Curr Opin Neurobiol 2004 14:423-7

Scott, Neuron 2005 48:455-64

Chandrashekar et al, Nature 2006 444:288-94

Gustation – sugar/amino acid receptors

Sweet and amino acids – determined by T1R genes (T1R1, T1R2 & T1R3)

- T1R receptors function as dimers
- T1R1+3 – amino acids (MSG & aspartate; “umami”)
- T1R2+3 – sugars (including saccharin)

Function as G protein coupled receptors (GPCR)

Tuned to individual compounds (site of ligand binding determines recognition of quality)

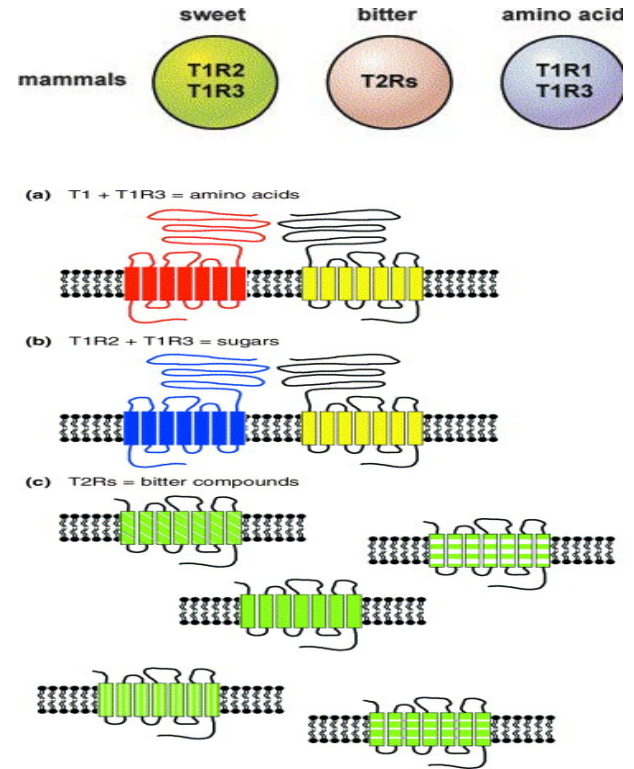
Knock out of T1R2+T1R3 causes loss of sweet

Sweet preference determined by T1R

Scott, Curr Opin Neurobiol 2004 14:423-7

Scott, Neuron 2005 48:455-64

Chandrashekar et al, Nature 2006 444:288-94



Gustation – bitter receptors

Bitter – determined by T2R genes (~25)

Different T2R receptors recognise different compounds e.g.

hT2R14 – picrotoxinin

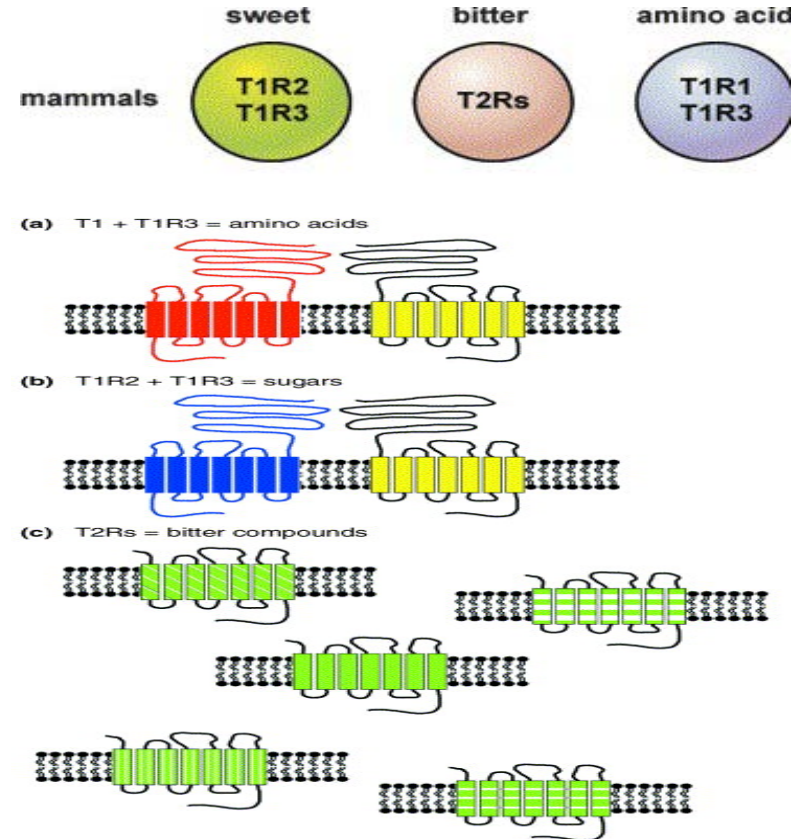
hT2R28 – phenylthiocarbamide

Most T2Rs expressed on the same TCR-
the cells are broadly tuned high
affinity bitter receptors on a single cell

Scott, Curr Opin Neurobiol 2004 14:423-7

Scott, Neuron 2005 48:455-64

Chandrashekar et al, Nature 2006 444:288-94



Taste – salt and sour

Salt: sodium channels? (receptor unknown)

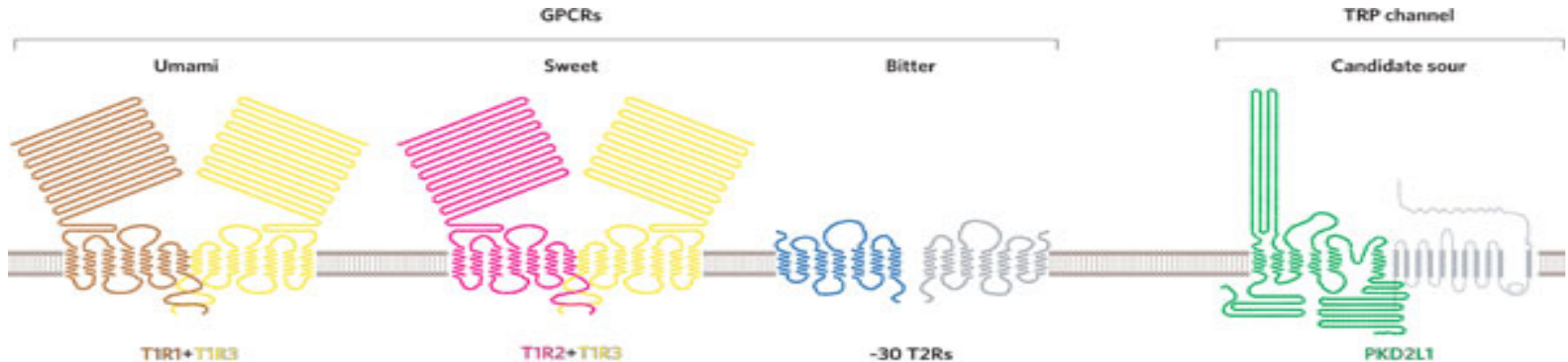
Sour: Acid sensing proton channels?

Calcium channels?

Chloride channels?

Potassium channels?

PKD2L1 (involved)



Umami

- Savory, desirable, enjoyable, good taste
- intensifies other taste sensations
- Amino acid rich foods, free glutamate
- Glutamate receptors:
 - T1R1/T1R3; mGluR4, mGluR1

Free Fatty Acid Receptors (FFAR)

- Fatty taste: role energy intake & taste/texture preferences
- Role: energy intake & appetite via secretion of insulin & incretin & sympathetic stimulation
 - Hara T, Kimura I et al. Rev Physiol Biochem Pharmacol 2013;Apr 30
- FFAR: G-protein coupled receptors (GPCR) oral cavity & GIT
- Medium & long chain FFAR GPR40 (Ffar1) & GPR120; on taste bud type I,II cells
- Animal study: FA: testing linoleic acid & oleic acid
- FFA also modify bitter taste, but not mediated by GPR40/120
 - Cartoni C Yasumatsu K, Ohkuri T et al. J Neurosci 2010;30:8376-82

Spicy Taste

- C-fibers/A δ fibers/neuropathy

Taste signaling & Neuropeptide Secretion

- Sweet, bitter, umami \uparrow calcium homeostasis modulator 1 (CALHMI) ion channel & \uparrow ATP release from taste bud
 - Taruno A, Vingtdau V, Ohmoto M et al. Nature 2013;495;223-6
- Taste stimulation yields different receptor cell signaling
- Tastant- \uparrow ATP & effect via K^+ & Ca^{2+} channels
- Sweet/umami: \uparrow GLP-1, NP-Y \downarrow glucagon
- Sour/salty: \uparrow NP-Y, no Δ GLP-1, glucagon
- Bitter: no Δ NP-Y, GLP-1, glucagon
- *NPY: neuropeptide-Y, GLP-1: glucagon-like peptide
 - Geraedis MC, Munger SD. J Neurosci 2013;33:7559-64

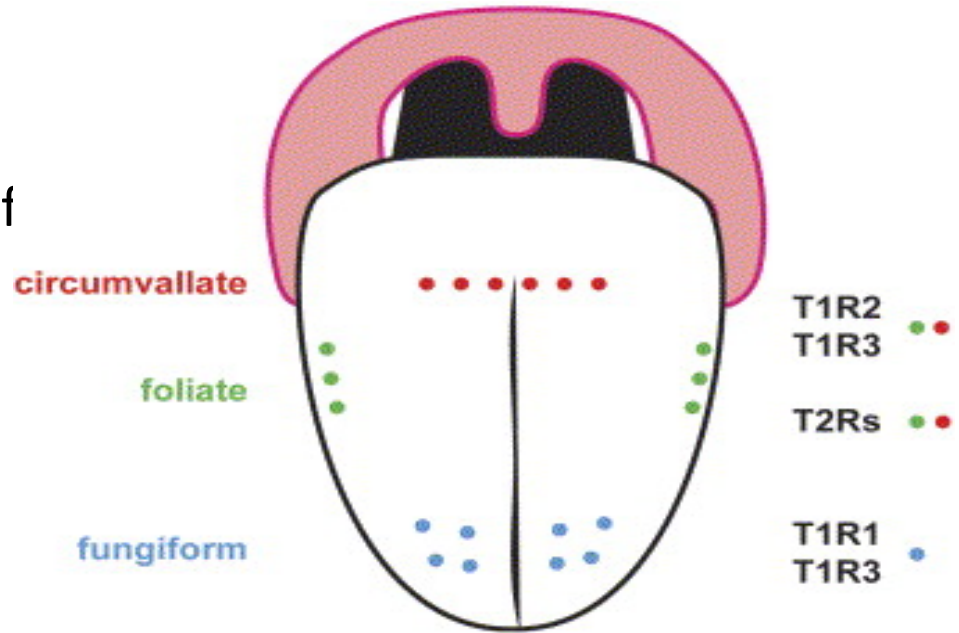
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Gustation – organisation of receptors

Spatial segregation of senses not evident in humans, although some nerves that synapse to T1R project to rostral aspects of the solitary tract nucleus (and T2R to caudal)

Possible segregation in mice, but not humans



Altered taste

Oral and URT disease (infection, malignancy)

Burning mouth syndrome

Hyposalivation

Iatrogenic

Drugs: Many!

Chemotherapy

Cyclophosphamide, Dacarbazine, Daunorubicin
Doxorubicin, 5FU, MTX, Platinum, Vinca alkaloids

Systemic disease

CNS (temporal lobe tumors , epilepsy)

GERD etc

Renal – chronic failure

Hepatic failure

Deficiency states (zinc)

Psychiatric (including hypochondriasis)

Symptom Burden in HNC: oral energy & protein intake

- 43 HNC pts, cross-sectional, prospective study
 - Median age 60; 97.7% Caucasian, 81% M; HNC Stage III 28%, Stage IV 63%; All RT HNC, mean 6862 Gy; CT 93%,
 - feeding tube 86%; tobacco 81%, alcohol 46%
 - VHNSS 2.0 24 hr diet dietary recall, protein, energy intake using Mypyramid.com
- Ganser H, Touger-Decker R, Parrott J. JSCC 2012; July 24

Altered taste and head and neck malignancy

Common – up to 100% - but may arise before treatment – due to tumor.
Review suggested up to 89% of patients prior to RT have some taste disturbance

Ruo Redda and Allis Canc Treat Rev 2006 32:541-7

Subjective assessment prior to RT suggested partial loss of bitter (35%), salt (18%) and/or sweet (6%)

Maes et al, Radiother Oncol 2002 63: 195-201

Taste change begins ~3 weeks and in some studies improves by 8 weeks of TX

Yamashita H, Nakagawa K et al Int J Radiat Oncol Biol Phys 2006;66:1422-9

Yamashita H, Nakagawa K. Et al. 2008

Second most common complaint in patients after 3 and 6 months post-RT HNC

Murphy BA, Epstein JB 2011

Radiotherapy-associated taste change

Effects on taste quality variable

- Loss of sweet first

- Bitter and salt>sweet

- 4 “conventional” qualities equally affected

- Umami affected

Mossman et al, 1979 5:521-8

Maes et al, Radiother and Oncol 2002 63:195-2001

Zheng et al, Fukuoka Igaku Zasshi 2002 93: 64-76

Shi et al, Auris Nasus Larynx 2004 31: 401-6

Yamashita et al, Head and Neck 2006 June 508-16

Ruo Redda and Allis Canc Treat Rev 2006 32:541-7

Yamashita H, Nakagawa K et al. 2008

Possibly reflecting:

- Method of assessment

- Radiotherapy dose & technique

Loss of umami may have the strongest correlation with QoL

Altered taste: head and neck malignancy

Radiotherapy taste changes highly variable:

“Soapy”

“Burning”

“Oily”

“Powdery”

“Chemical”

“Awful”

Impact of taste change:

Reduced dietary intake

Weight loss

Reduced QoL

Poor(er) outcomes

Radiotherapy-associated taste change

Temporal effects variable

Maximum loss of taste at 2/12, returned by 24/12

Maes et al, Radiother Oncol 2002 63: 195-201

Taste disturbance still reported at 7 years post-RT

Mossman et al, Int J Radiat Oncol Biol Phys 1982 8: 991-7)

Normal taste by 6/12

Zheng et al, Fukuoka Igaku Zasshi 2002 93: 64-76

4 taste cues reduced by 3/52, returned to normal by 4-8/12

Yamashita et al, Head and Neck 2006 June 508-516

4 taste cues reduced within 1/12, normal by 6/12

Sandow et al, 2006 J Dent Res 2006 85: 608-611

Possibly reflecting:

- Method of assessment

- Radiotherapy dosage

- Radiotherapy technique

- Patient numbers

Taste Change in Breast Cancer

- 25 pts, TX docetaxel or paclitaxel or within 6 months of CT
- most common PRO: taste change (8/10 docetaxel; 3/15 paclitaxel)
- Dysguesia: 55%; bad taste 27%, hypoguesia 45, hyperguesia 9%
- Taste change affect oral intake, irregular eating schedule, ↓ interest meal preparation
- Behaviors: new recipes, strongly flavored foods, food cravings, candy before meals, adding lemon, sweetened drinks, plastic utensils, drink with straw, brush teeth & tongue, baking soda/salt rinsing, antibacterial mouthwash
- Self management: ↑ caloric intake, poor eating behaviors, ↑ weight & association of obesity with poor outcomes
 - Speck RM, DeMichele A, Farrar JT et al. Support Care Cancer 2013;21:549-55

Nutritional issues & body weight in allo-BMT long-term survivors

- 441 BMT survivors of BMT, NSW Australia

Symptom	<2 yrs BMT n=58	2-5 yrs BMT n=159	>5 yrs BMT n=224
Nausea	8(13.8%)	21(13.2%)	21(9.4%)
Vomiting	3(5.2%)	10(6.3%)	6(2.7%)
Constipation	10(17.2%)	15(9.4%)	41(18.3%)
Diarrhea	11(19.0%)	29(18.2%)	43(19.%)
Taste change	26(44.8%)	53(33.3%)	55(24.5%)
Smell change	19(32.8%)	34(21.4%)	35(15.6%)
Poor appetite	16(27.6%)	29(18.2)	40(17.9%)
Mouth ulcers	21(36.2%)	46(28.9%)	77(34.4%)
Dry mouth	26(44.8%)	65(40.9%)	93(41.1%)
Median # symptoms	2(0-9)	1(0-9)	1(0-7)

Smith J, Poon C, Gilroy N et al. Support Care Cancer 2017;25:137-4

Prevalence of CT-related problems & HRQOL

- 363 (43% response rate); mixed diagnoses, CT for “cure”
- Most prevalent c/o: fatigue (90%); change in smell/taste (69%)

Rank	Problem	% affected	Severe	Moderate	Mild
1	Fatigue	90%	11%	37%	42%
2	Change in taste/smell	69%	11%	24%	34%
4	Trouble with sleep	55%	9%	21%	29%
5	Low mood	56%	4%	16%	30%
9	Loss appetite/interest in food	54%	5%	17%	32%
10	Concentration, forget, confused	52%	3%	11%	38%
12	Sore mouth/tongue	46%	6%	12%	20%
13	Diarrhea	39%	4%	12%	28%

- Related to HRQOL social/emotional domains
 - Wagland R, Richardson A, Ewings S et al. Support Care Cancer 2016;24:4901-11

Oral complaints & dental care in SCT

- Survey: 101 SCT adult pts (37% allo) (95% response of survivors[possible bias]);
- 88 patients dentists (59% response)
- Time since SCT mean 19 mos (range: 8-31)
- Allo SCT: Mean max mucositis score 6.6 (sd=3.3)

Complaints	Acute	Chronic
Dry mouth	70%	56%
Taste change	86%	33%
Mucositis	96%	11%
Trismus	14%	7%

Taste and Smell in SCT

- 23 pts (16 at all time points): baseline, Day 30, Day 80
- Taste: 0.32 M NaCl; 0.0056 & 0.018 M citric acid; 0.3 M sucrose;
Olfactory: NIH toolbox Odor Identification test; QOL
- ↓ sensitivity for NaCl, citric acid on D30
- ↑ sensitivity sucrose D30
- Taste largely recovered by D80
- Olfactory scores unchanged baseline to D30
- QOL improved by D80, although some oral symptoms remain
 - Abasaheed R, Coldwell SE, Lloid ME, et al. JSCC 2018;Apr 27

Oral health & QOL in cancer patients in hospice

- 104 terminally-ill CA pts (2.5-3 wk life expectancy); median age 66.0; M 40.8%, F 59.2%
- Oral Problems Scale (OPS): xerostomia, oral pain, taste change & functional/social impact on QOL; oral exam
- Hyposalivation (98.1%), erythema (50%), ulceration (20.2%), fungal infection (35.6%), other oral problems (44.2%).
- Xerostomia, taste change & oral pain impact QOL ($p < 0.001$, < 0.042 & $p < 0.001$, respectively)
- Oral pain significant social impact ($p < 0.001$); ulcers \uparrow pain
- Erythema associated with fungal infection & ulceration ($p < 0.0001$)
 - Fischer DJ, Epstein JB, Yao Y, Wilkie DJ. Supp Care Cancer 2013

Flavor

- combination of sensory functions:
 - Taste, texture, temperature, smell, visual, memory
- Basic qualities: Sweet, bitter, salty, sour, umami
- Other qualities: fat, spicy, water
- Umami ~ good/desirable flavor may have strongest correlation with QOL
- Impact:
 - Interest in food
 - altered food intake leading to dietary deficiencies or weight loss/weight gain
 - Impaired quality of life

Chandrashekar J, Hoon MA, Ryba NJ. Nature. 2006

Yamashita H, Nakagawa K et al. Oral Oncol. 2008

Shi HB, Masuda M, et al. Auris Nasus Larynx 2004

Moskowitz PA, Friedman JD, Hoon MA. 2011

Fatty Acid Taste

- Fatty taste thought to mediate important energy intake
- Medium & long chain FA receptor GPR40 (Ffar1) & GPR120; on taste bud type I,II cells
- Animal study: FA testing linoleic acid & oleic acid
- IHC, nerve recording, behavioral outcome affected
- FA also shown to modify bitter taste, but not mediated by GPR40/120
 - Cartoni C Yasumatsu K, Ohkuri T et al. J Neurosci 2010;30:8376-82

Dietary Adaptations/Maladaptations

- ↓ quantity of food
- ↓ high fiber foods
- ↓ vitamin, mineral, protein & energy
- ↑ fat content
- ↑ caffeine & sugar
- ↑ caries risk

Impact:

- ↓ interest in food
- altered food intake
- dietary deficiencies, weight loss

Importance of Oral Health Outcomes:

- Oral health conditions result in:
 - Altered function
 - ↑ Symptom burden
 - ↓ quality of life
 - ↑ costs
- Oral health influences general health:
 - Pain, taste, dysphagia; nutritional deficits
 - Aspiration may cause pulmonary disease
 - Periodontitis associated with CAD
 - Psychosocial impact: pain, esthetics, social function
- Changing Expectations:
 - ↑ HNC in younger adults
 - Retention & esthetics of dentition is important

Taste in Chemotherapy

- Consecutive breast CA pts adjuvant CT
 - baseline, 6th cycle, 6 & 12 months
 - Taste disturbances common during CT v. baseline & v. to no CT
 - During CT: dysgeusia (metallic or drug taste, 33%) + hypogeusia (22%)
 - 6 months F/U: taste change (20%)
 - 12 months F/U: most reported taste change: hypogeusia (16%)
 - PI/GI ↑ during CT; mucositis: ~20%, ulcer 16%
 - Taste the most distressing oral symptom in 22% during CT, and in 10% at 12 months
- Jensen SB et al. Oral Surg 2008

Taste Change in Breast Cancer

- 25 pts on docetaxel or paclitaxel or within 6 mos of CT
- most common PRO: taste change (8/10 docetaxel; 3/15 paclitaxel)
- Dysguesia: 55%; bad taste 27%, hypoguesia 45, hyperguesia 9%
- Taste change affect oral intake, eating schedule, ↓ interest meal preparation
- Behaviors: new recipes, strong flavored foods, food cravings, candy before meals, adding lemon, sweetened drinks, plastic utensils, drink with straw, brush teeth & tongue frequently, baking soda/salt or mouth rinsing
- Patient adaptations: some +/- : ↑ calorie intake, poor eating behaviors, ↑ weight
 - Speck RM, DeMichele A, Farrar JT et al. Support Care Cancer 2013;21:549-55

Taste & Smell Change in CT

- OutPt 518 CT subjects, various solid CA, questionnaire
- TSC: 75%, > ♀ 79% v ♂ 59% , younger pts
- TSC > breast CA; CT: cyclophosphamide, 5FU, epirubicin; venorelbine
- Taste change: salty 41%, sweet 36%, bitter 24%, sour 21%, other 48%
- Smell change: 49 %, greatest perfume, cooking smells
- Impact of TSC associated with (OR):
nausea 4.0, vomiting 1.7, oral problems 4.0,
appetite loss 3.2 , depression 1.8

Taste & Olfaction in BC patients

- 69 BC patients, mean age 52.4 yrs, 24 post-menopausal, post-sx 62, pre-CT
- Symptoms, smell (“Snffin’ Stiks”) & taste testing (taste strips)
- Results comparable to normative data:
- No difference in odor threshold, odor detection, ↓sensitivity for sour, no change for salt, sweet, bitter; ↑ T size associated with ↓smell, but not taste; correlation with bitter taste & Her2+
 - Steinbach S, Hundt W, Zahnert T et al. Support Care Cancer 2010;18:707-13

Taste change in cancer patients

Under-reported

Influence of xerostomia: Correlations possible

Mossman et al Int J Radiat Oncol Biol Phys 1982 8: 991-7

Inokuchi et al, Practica Oto-Rhino-Laryngologica 2002 95: 1091-6

Zheng et al, Fukuoka Igaku Zasshi 2002 93: 64-76

Tongue volume: Correlations suggested

Fernando et al, Clin Oncol (R Coll Radiol) 1995 7: 173-8

Yamashita et al, Head and Neck 2006 June 508-516

Variability: unusual report of long term complete loss despite ½
tongue being spared

1) Strategies to Improve Taste and Odor Abnormalities

- Avoid use of metallic utensils
- ↓ food with metallic or bitter taste (eg: red meat, coffee, tea)
- ↑ high-protein, mildly flavored foods (chicken, fish, dairy products, eggs)
- ↑ seasoning & spices to enhance flavors
- Serve foods at cold temperature
- Practice good oral hygiene
- If dry mouth provide saliva stimulation

2) IMRT

- Aim: to spare radiation of salivary glands, and reduce high dose RT to oral tissues when possible

Therapy

Dietary counselling/modification

Seasoning, avoid unpleasant foods, extend dietary choice (pleasing color, form, smell, texture)

Peregrin J Am Diet Assoc 2006 106: 1536-40

Food preparation: spice/flavoring, increase umami flavor

Manage xerostomia

Manage oral disease

Zinc sulphate

Reduced severity & duration of taste dysfunction (18 patients)

Ripamonti et al, Cancer 1998 82: 1938-45

But benefit (NS) observed in larger study (169 patients; lower dose)

Halyard et al, Int Radiation Oncology Biol Phys 2007 67: 1318-22

Medications: clonazepam, gabapentin, megestrol, THC (Marinol), CBD

Thorne T, Olson K, Wismer W. JSCC 2015;23:284

Manage Oral/OPC pain and nausea if present

Supplements and Taste

- Zinc may promote taste bud proliferation
- Zinc (50 mg/TID) may affect taste independent of serum zinc levels
 - Heckmann SM, Hujoel P, Habiger S. J Dent Res 2005;84:35-8
 - Takaoka T, Sakukura N, Ueda C. Auris Nasus Larynx 2010;37:190-4
- Alpha lipoic acid may affect neuropathy
- Alpha lipoic acid (200 mg tid)for taste disorders: 91% improved, 46% resolved
 - Femiano F, Scully C, Gombo F. Int JOMF Surg 2002;31:625-8

Study	Design	Regimen	Outcomes
Mossman, 1978	Case series n = 7, post HN RT	25 or 100 mg / day zinc for 2-6 months	Improvement in objective taste
Silverman & Thompson, 1984	Case series n = 30; post HN RT	100-150 mg / day zinc for at least 1 month	Improvement in subjective taste
Silverman et al, 1983	RCT n = 19; pre HN RT	18 mg qd zinc for duration of RT	No difference in objective taste Earlier recovery of subjective taste
Ripamonti et al, 1998	RCT n = 18; in HN RT	45 mg /d zinc until 1 month post RT	Less objective taste disturbs during RT. Earlier recovery of objective taste
Halyard et al, 2007	RCT n = 169; pre HN RT	30 mg /d zinc During RT and 1 month after	No difference in subjective taste disturbance No difference in recovery of taste
Lyckholm et al, 2012	RCT n = 58; during chemo	220 mg bid zinc During chemo	No difference in taste alterations Longer time to recovery of smell alterations

4) OTHER: WHAT'S NEW?

- Natural substances: Synsepalum dulcificum (miracle fruit)
→ binds to taste receptors to generate a sweet sensation, thus masking some unpleasant tastes for a short duration
- Chlorhexidine may block bitter taste receptor
- Marinol (THC cannabinoid) → enhances food enjoyment via endocannabinoid receptors that stimulate the orosensory reward pathway
- Megace: 20-40 mg BID

Zinc Sulfate Trial in HN RT

- 169 pts randomized to Zinc SO₄ 45 mg/d during RT + 1 month after v placebo
- Taste outcomes assessed with Wickham questionnaire
(Wickham RS Oncol Nurs Forum 1999;26:697-706)
- 73% on Zinc v 84% reported taste alterations (p=0.16)
- Complex taste change: absence 16%; bitter 8%; salt 4%; sweet 5%; metallic taste 10%; written comments soapy, oily or burning taste
- Halyard MY, Jatoi A, Sloan JA, et al. Int J Radiat Oncol Biol Phys 2007;67:1318-22
- Benefits on taste reported; taste testing: taste thresholds
- Ripamonti C, Zecca E, Brunelli C et al. Cancer 1998;82:1938-45

Clonazepam

- Gabanergic drugs modify taste in animal study
 - Starostik MR, Rebello MR, Cotter KA. PLoS One 2010;5:e13639
- Clonazepam: gaba A agonist affect taste change associated with BMS
 - Grushka M, Epstein J, Mott A. Oral Surg Oral Med Oral Pathol 1998;86:557-61

THC & Chemosensory Disorders

- 46 pts, advanced cancer; 21 completed study, 11 dronabinol (Marinol) [THC], 10 placebo, RX 18 days
- 2.5/5.0/10 mg bid
- THC indicated: nausea, appetite
- THC v placebo:
 - ↑ appreciation of food 73% v 30%
 - ↑ taste 55% v 10%
 - ↑ appetite $p < 0.05$, ↑ sleep quality,
 - no overall Δ QOL

- Brisbois T. Ann Oncol 2011
- De Luca M Neuropharmacol 2012

Megestrol

- RT +/- CT advanced cancer; 100 pts, randomized trial megestrol, PROs
- 46 megestrol during RT, 4 after RT; 50 placebo x 3 mos
- no difference acute toxicity of RT; acute toxicity associated with weight loss placebo but not megestrol
- megestrol ↑appetite, ↑taste, ↑weight ($p=0.000$); ↑smell ($p=0.02$);
- no SE
 - Erkurt E, Erkisi M, Tunali C. J Exp Clin Cancer Res 2000;19:431
- Megace 480 mg/d
 - Thorne T, Olson K, Wismer W. JSCC 2015;23:284

Local measures for blocking abnormal taste

- Food preparation:
 - herbs, spices, sweetener, acid to food
- Masking agents:
 - mouthwashes, candy, gum
- Chelating/blocking agents:
 - chlorhexidine may block salt & bitter taste
- Miracle Fruit (*Synsepalum dulcificum*):
 - Glycoprotein “miraculin”, may modify bitter and sour to sweet taste; block bitter?
 - Thorne T, Olson K, Wismer W. Support Care Cancer 2015;23:2843-51
 - Joma I, Renken RJ, Ter Horst GJ. Cancer Treat Rev 2015;41:179-86
 - Swamy KB, Hadi SA, Sekaran M. J Med Food 2014;17:1165-9

Local measures for blocking abnormal taste

- Blocking bitter taste: TAS2R2 receptor inhibitors; below affect some bitter receptors, but not all
 - 4-(2,2,3-trimethyl-cyclopentyl) butanoic acid (GIV3727)
 - gamma-aminobutyric acid
 - 6-methoxyflavones
 - probenecid
 - MSG
 - Na,Na-bis(carboxymethyl)-1-lysine (BCML)
 - phosphatidic acid-tactoglobulin
 - adenosine 5'-monophosphate
- Blocking sweet taste:
 - Lactisole
 - Gymnemic acid
- Blocking sweet and bitter: Chlorhexidine
- Changing acid to sweet/blocking bitter: Miracle fruit?

Miracle Fruit

- Miracle Fruit (*Synsepalum dulcificum*):
 - Glycoprotein “miraculin” may modify bitter and sour to sweet taste
 - Binds to T1R2-T1RX as antagonist at neutral pH & agonist at acid pH
 - Joma I, Renken RJ, Ter Horst GJ. Cancer Treat Rev 2015;41:179-86
 - Swamy KB, Hadi SA, Sekaran M. J Med Food 2014;17:1165-9
 - Koizumi A, Tsuchiya A, Nakajima K et al. Proc Natl Acad Sci 2011;108:16819-24
 - Transduce acidic to sweet signal; mask unpleasant taste, increase palatability of some foods
 - Taste improvement Miraculin v placebo x 2 wks in 8 CT pts on CT cross over study with improvement on active arm
 - Wilken MK, Satiroff B A. Clin J Oncol Nurs 2012;16:E173-7

Prevention and Treatment of Neuropathy

- No proven prophylaxis
- Management: based on pain management of neuropathic pain
- Centrally acting medications:
 - clonazepam, gabapentin, pregabalin, duloxetine, tricyclics
- Topical agents:
 - receptor blocking/stimulating agents
 - centrally acting medications, trial: baclofen, amitriptyline, ketamine
- Nerve stimulation

Evidence-Based Strategies for Oral Complication of Cancer Treatment

knowledge of the burden of illness, prevention and treatment of oral complications associated with cancer therapies is necessary

systematic reviews of the most common oral complications were completed by the Oral Care Study Group of MASCC/ISOO.

Management recommendation and guideline classification was based on criteria of the ASCO rating the level of evidence and grade of recommendation

Resources:

- MASCC.com
- NCI-PDQ: oral care, mucositis
- Epstein JB, Barasch A. Taste disorders in cancer patients: Pathogenesis, and approach to assessment and management. *Oral Oncol* 2010;46(2):77-81.
- Epstein JB, Murphy BE. Oral health and survivorship: Late effects of cancer and cancer therapy. In: *The MASCC Textbook of Cancer Supportive Care and Survivorship*. Olver IN (Ed). Springer, New York, ISBN 978-1-4419-1224-4 2010; pp 399-406.
- Davies AN, Epstein JB (Eds). *Oral Complications of Cancer and its Management*. Oxford University Press Inc, Great Clarendon Street, Oxford OX2 6DP; Oxford University Press Inc, New York, 2010; ISBN 978-0-19-954358-8.

Dysgeusia (5)

Dysgeusia: an abnormal or impaired sense of taste, an unpleasant alteration in taste, or a distortion or perversion of taste

Mean weighted prevalence of dysgeusia:

- Chemotherapy only = 56.3%

- Radiotherapy only = 66.5%

- Combined RT and CT = 76%

Management:

- Zinc gluconate (Level of evidence II, recommendation grade C)

- Suggestion to NOT use zinc gluconate to prevent dysgeusia in HNC patients, although this is beneficial in a non-cancer idiopathic dysgeusia cohort

- Amifostine (Level of evidence II, recommendation grade B)

- Recommend NOT to use amifostine solely for the prevention of dysgeusia HNC patients

- Dietary counseling (Level of evidence II, recommendation grade B)

Oral Fungal Infection (6)

Oral candidiasis: the majority of oral fungal infections

presentation: pseudomembranous candidiasis, erythematous candidiasis, hyperplastic candidiasis, angular cheilitis

Weighted prevalence of clinical oral fungal infection (all oral candidiasis)

pre-treatment = 7.5%

during cancer treatment = 39.1%

after the end of cancer therapy = 32.6%

Weighted prevalence of oral candidiasis by cancer treatment

during head and neck radiation therapy = 37.4%

during chemotherapy = 38%

Weighted prevalence of oral colonization with fungal organisms

Before cancer treatment = 48.2%

during cancer treatment = 72.2%

after cancer treatment = 70.1% .

Weighted prevalence of oral fungal colonization by cancer treatment

during chemotherapy = 72.8%

during radiation therapy = 74.5%

Oral fungal Infection (5)

Management

Weighted prevalence of clinical oral fungal infection during cancer therapy by preventive treatment regimen

Fluconazole = 1.9%

Amphotericin = 2.3%

Itraconazole = 1.5%

Nystatin alone = 6%

Clotrimazole and nystatin = 14.6%

Amifostine = 28.9%

Placebo/No treatment = 20.3%

Topical antifungal agents (level of evidence II, recommendation grade C)

inconsistent efficacy of topical antifungal agents as prophylaxis. No recommendation possible.

Systemic antifungal agents (level of evidence I, recommendation grade A)

Recommend fluconazole for the prevention of oral candidiasis in cancer therapy.

Oral Viral Infection (7)

Prevalence of HSV oral and perioral infection:

Weighted prevalence in patients treated with chemotherapy for hematologic malignancies

Patients with oral ulcerations – sampling oral ulcerations = 49.8%

Weighted prevalence in patients treated with radiotherapy

Patients with radiotherapy only- sampling oral ulcerations * = 0%

Patients with radiotherapy + CT- sampling oral ulcerations = 43.2%

Management

Acyclovir & valacyclovir recommended for the prevention of HSV (Grade of recommendation A, level of evidence I)

Prevention: acyclovir (800 mg/day) or valacyclovir (500-1000 mg/day)

valacyclovir may be superior to acyclovir in toxicity & cost (depends on the route of administration of acyclovir—PO or IV)

* - Simple prevalence is presented as this finding is based on a single report in the literature.

Dental Disases (8)

- Weighted prevalence for dental caries in patients treated with cancer therapy
 - All studies = 28.1%
 - Chemotherapy only = 37.3%
 - Post-radiotherapy = 24%
 - Post chemotherapy and radiotherapy = 21.4%
- Weighted prevalence severe gingivitis in patients undergoing chemotherapy = 20.3%
- Weighted prevalence dental infection/abscess in patients undergoing chemotherapy = 5.8%
- Management
 - Recommend fluoride to prevent dental caries in patients who are post-radiotherapy. Effective regardless of the type of delivery method. (Level of Evidence II, Grade of Recommendation B).
 - Recommend chlorhexidine to improve oral hygiene, potential side effects: tooth staining, increased calculus, taste changes (Level of Evidence: II, Grade of Recommendation: B.)
 - Suggest the use of resin-modified glass ionomer, composite resin or amalgam restoration in patients who have been treated with radiotherapy (Level of Evidence III, Grade of Recommendation B).
 - No guideline possible due to the lack of well designed studies regarding the benefits of toothpaste, pre-cancer therapy dental intervention, honey, and cheese on dental health (Level of Evidence III, Grade of recommendation C).

Osteoradionecrosis (ORN) (9)

- Weighted prevalence in conventional RT = 7.4%
- Weighted prevalence in intensity modulated RT = 5.2%
- Weighted prevalence in RT and chemotherapy = 6.8%
- Weighted prevalence in brachytherapy = 5.3%
-
- The majority of cases involve the mandible.
-
- Management
-
- Practitioners should utilize their clinical experience and expertise in determining optimal management for their patients relative to ORN of the mandible or the maxilla.
-
- No guideline is possible regarding the use of prophylactic HBO therapy for the prevention of ORN in patients requiring post-RT dental extractions
(Level of evidence III, recommendation grade C)
-
- The use of single therapy HBO therapy for the treatment of ORN is NOT recommended (Level of evidence II, recommendation grade B)
-
- No guidelines possible for other prevention and treatment strategies for ORN
-

Treatment for Oral Malodor ¹

- Management of local dental pathosis
 - restorations, caries or pulp pathology; periodontal disease; denture hygiene
- Management of oral soft tissue conditions
- Diagnosis/Management of ENT pathosis
 - sinusitis, tonsoliths, post nasal drip)
- Dietary suggestions:
 - Avoid odiferous foods
 - Avoid tobacco and alcohol
 - Reduce the consumption of red meat and dairy products
 - Avoid staying hungry -healthy snacks between meals
- Good oral hygiene
 - Home care including brushing, flossing, denture care, tongue scraping
 - Regular professional cleaning

Treatment for Oral Malodor ²

- Maintain mouth moisture
 - hydration
 - Stimulation: sugarfree gum/candy
 - Sialogogues
- Antimicrobial mouthwashes
 - Chlorine dioxide, cetyl pyridinium chloride, phenolic oil, zinc chloride, triclosan, chlorohexidine etc
- Medical evaluation of systemic conditions

Management of Olfactory Disorders

Pharmacotherapy

- Systemic & topically applied corticosteroids for mucosal edema/ nasal polyps
- Antibiotics, decongestants & antihistamines for chemosensory loss due to sinus infection & allergic rhinitis
- Benzodiazepines, tricyclic antidepressants, anticonvulsants may be helpful:
 - clonazepam 0.5-2 mg hs
 - amitriptyline 25-100 mg hs
 - gabapentin 300-1,800 mg per day

Management of Olfactory Disorders

Surgery

- Endoscopic nasal/sinus surgery

Miscellaneous

- counseling on smoke & natural gas detection
- labeling of food to track spoilage
- Baseline & repeat chemosensory testing

*olfactory function may take years or may never recover, following post-viral infection or head trauma

Conclusions: Taste and Smell

Impact upon QoL

Known physiology does not match observations of post RT taste dysfunction –
why selective in quality?

Volume of RT may correlate with taste dysfunction

Salivary function seems a part of the presentation: (taste dysfunction resolves,
xerostomia does not or xerostomia resolves and taste does not)

Zinc sulphate has uncertain effects

Methods that lessen tissue damage may be the way forward (prevention)

Summary: Report to the Nation on Status of Cancer 2013

- ↓ Death rates 2000-2009: 1.8%/yr M, 1.4%/yr F; <14yrs age 1.8%/yr
 - ↓ overall deaths due to cancer for all but melanoma, liver, pancreas & uterus
 - 2000-9 ↓ incidence overall cancers 0.7%/yr men; stable in women, ↑0.6% children
 - 2000-9 ↑ incidence of HPV OPC white men/women; vulva white & black women
 - US: 48.7% girls 13-17 HPV vaccinated, 32% 3 doses; Canada 50-85%, UK/Australia 70%
 - Obesity related to 33% of cancers
- Jemal A, Simard EP, Dorell C et al JNCI 2014;105

Dietary Modifications for Cancer Patients

Diet	Texture Modification
Regular diet	All foods allowed
Dysphagia diet, Advanced	Soft-solid foods that require chewing
Dysphagia diet, mechanically altered	Cohesive, moist, semisolid food, limited chewing required
Dysphagia diet, pureed	Homogenous, cohesive, pudding-like
Liquid diet	Liquid supplements

Epstein JB, Huhmann M. J Am Dent Assoc 2012;143:588

National Dysphagia Diet

Diet Consistency	Description
NDD-1 (Dysphagia Pureed)	Soft, pudding-like consistency, smooth, no lumps
NDD-2 (Dysphagia mechanically altered)	Moist, soft, textured (eg: finely diced meats, soft-cooked vegetables, canned fruit, moist cereals)
NDD-3 (Dysphagia advanced)	Most regular foods, except very hard, sticky or crunchy
Liquid consistencies	
Spoon thick	thickened to pudding consistency; remain on a spoon in a soft mass
Honey-like	thickened to consistency of honey, flow off a spoon in a ribbon
Nectar-like	consistency that coats and drips off spoon
Thin liquids	All liquids

Liquid Nutritional Supplements

Type	Description	Examples
Ready to drink liquid nutritional	Premixed liquid	Ensure, Boost, Enlive, Resource Breeze, Isopure Plus
Milk-based	Power added to milk	Carnation Instant Breakfast (with/out sugar), Scndishake, protein powder
Disease-specific liquid	Premixed liquid, disease specific ingredients	Diabetic: Glucerna, Boost Glucose Control Renal: Nepro, Suplena, Renalcal
Modular	Powder or liquid add to food (protein or caloric supplement)	Liquid: Benecalorie, Promod, Pro-stat Powder: Beneprotein, Unjury Protein

Dietary Interventions: Late complications of HNC Therapy

Complication	Dietary Intervention
Loss of Appetite	Small, frequent meals; limit to non-carbonated beverages between meals, liquid supplements
Taste change	Tart food (citrus if tolerated), flavorful seasoning, marinate meats, chicken, fish in fruit juice, soy sauce, sweet wine, Italian dressing, add umami flavors
Mucositis	Avoid spicy, acidic, rough, salty foods
Hyposalivation	Soft, moist foods easy to swallow (sakes, bananas, applesauce, noodles, ice cream, yoghurt, eggs, gravy, broths, Chop, puree, blender foods; drink liquids with meals Avoid dry foods, simple sugars
Trismus/dysphagia	Soft foods, small bites, blender, supplements
Caries Risk	Avoid sugar sweetened drinks, gum, candy; fruit and juice with meals, pair cariogenic foods with cariostatic (peanut butter, cheese, milk, cereal, sweets only with meals, xylitol sweetner Brush teeth before meals

Enteral Feeding

Route	Indications
Gastric Nasogastric tube	Short term, local irritation
Percutaneous (endoscopic) Gastrostomy Tube (PEG)	Endoscopically place tube, least invasive permanent feeding tube
Gastrostomy tube	Surgically place tube, placed during SX or if endoscopic placement not possible
Small bowel	
Percutaneous endoscopic jejunostomy tube	Endoscopically place tube, used if esophagus or gastric SX planned
Jejunostomy tube	Surgically placed tube, placed during SX or if endoscopic placement not possible

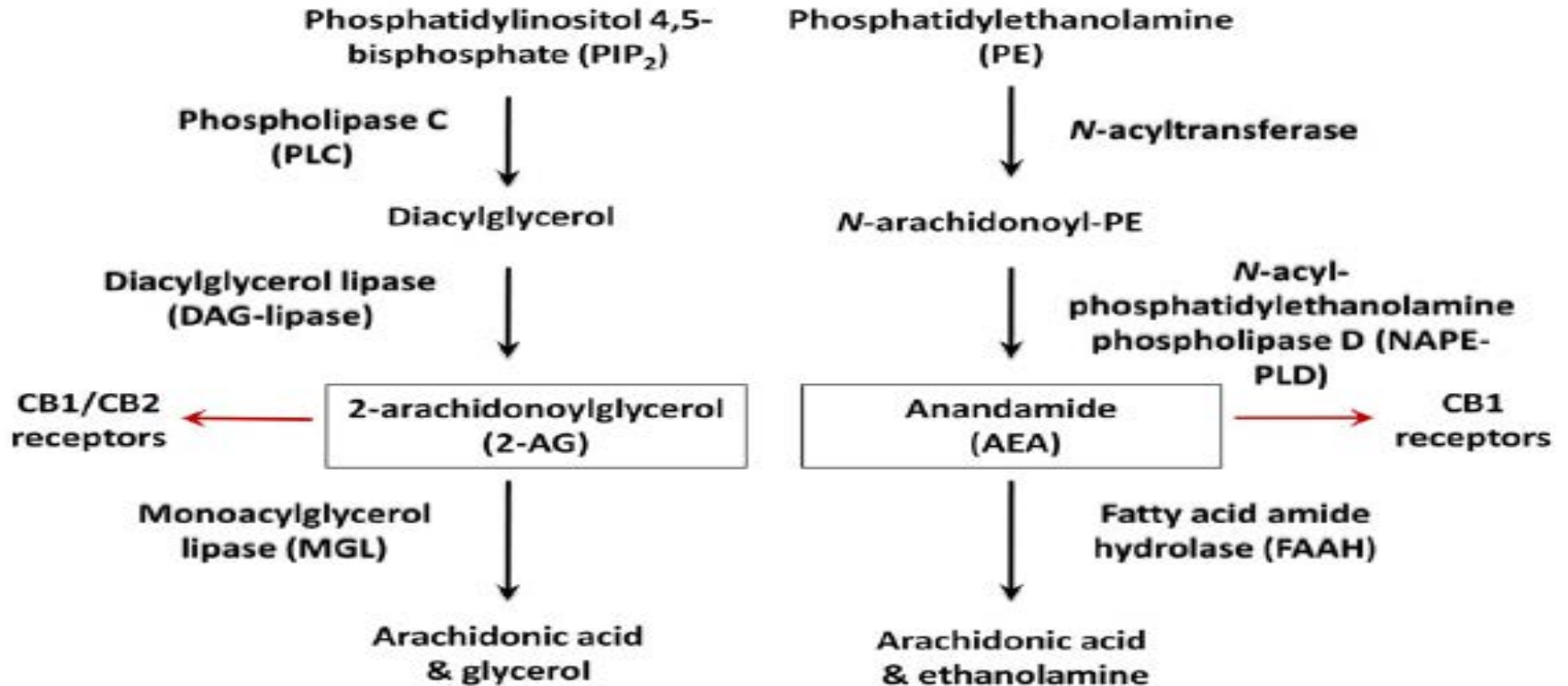
Approach to management:

- If it works, keep doing it...
- If it doesn't work, stop doing it....
- If you don't know what to do, don't do anything...
- (And of course don't refer to a surgeon! [unless surgery is needed])

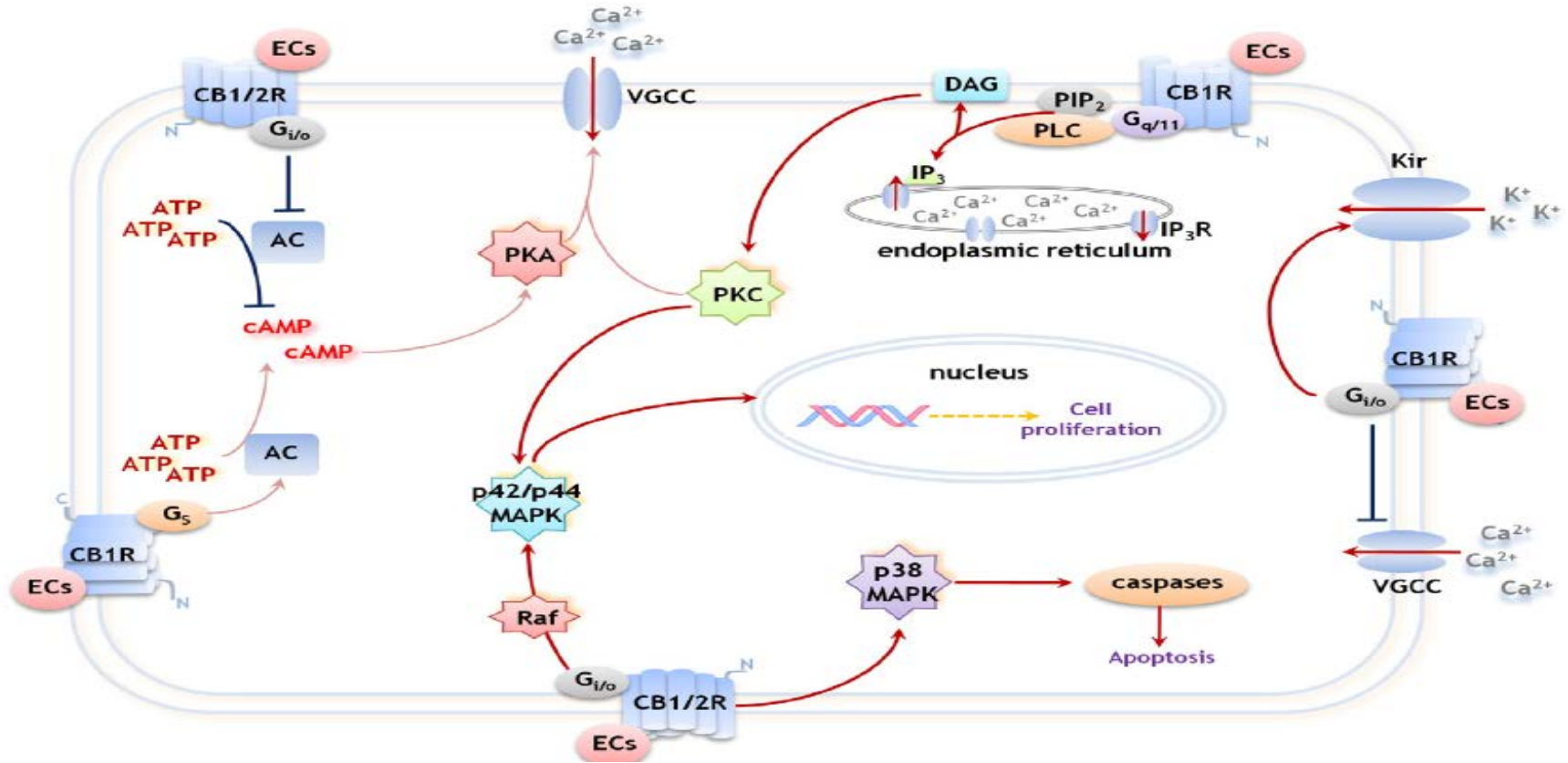
Cachexia/anorexia in Cancer patients

- up to 90% of advanced cancer
- Loss of adipose tissue/muscle mass
- Cancer biology, tumor growth
- Therapy: nausea, vomiting, flavor, appetite
- Change in taste, lack of hunger, lack of food enjoyment
- ↑ inflammatory cytokines associated with: ↓ wght, fatigue/energy; physical/cognitive decline
- Mouth condition (dental status), mucositis, saliva function
- Taste/smell/touch/temperature

Metabolism of 2-AG and Anandamide



Pathways of Cannabinoid Receptor activation



Blue line-inhibition; Red line-↑ activation

Legend to Table on Signaling Pathways of CB1/2

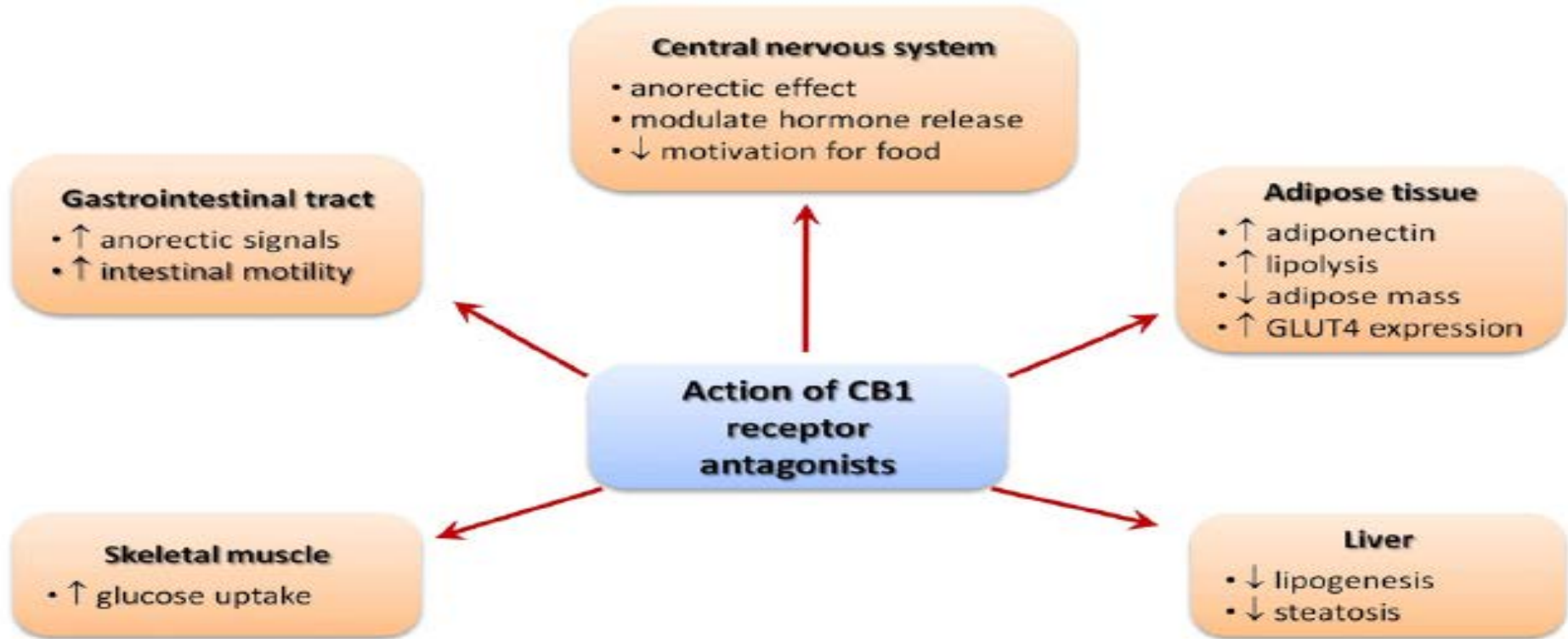
Fig. 2. Signalling pathways downstream of cannabinoid receptor activation. The schematic shows the main pathways activated by CB1 and CB2 receptors following binding of endocannabinoids (ECs). A red solid arrow shows CB1 receptor-induced activation of an inwardly rectifying potassium channel (Kir) current that decreases excitability, resulting in inhibition of voltage gated calcium channels (VGCC) and inhibition of Ca^{2+} influx, as shown by the solid blue line. Red solid arrows also demonstrate activation of p38 and p42/p44 mitogen activated protein kinases (MAPKs) following CB1/2 receptor activation. The p42/p44 isoforms of MAPK can stimulate cellular proliferation, while p38 MAPK activates caspases to induce apoptosis. The solid blue line downstream of CB1 and CB2 receptor-evoked $G_{i/o}$ activation indicates inhibition of adenylate cyclase (AC) and subsequent reductions in cyclic AMP (cAMP). The lighter pink lines demonstrate that under certain circumstances CB1 receptors may stimulate AC via G_s and the increased cyclic AMP can activate PKA, which may phosphorylate VGCCs to allow Ca^{2+} influx (pink lines). Another pathway through which Ca^{2+} may be elevated is via CB1 receptor activation of phospholipase C (PLC) via $G_{q/11}$ to generate inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) through phosphatidyl bisphosphate (PIP_2) hydrolysis (solid red arrows). IP_3 mobilises Ca^{2+} from the endoplasmic reticulum following binding to IP_3 receptors (IP_3R) and DAG activates protein kinase C (PKC) which may phosphorylate VGCCs to allow Ca^{2+} influx. PKC may also activate p42/44MAPKs to induce cell proliferation.

Cannabinoids and Taste

Cannabis in Cancer Cachexia-Anorexia

- Systematic review: 26 papers
- Tetrahydrocannabinol (THC), cannabidiol (CBD)
- Routes of delivery: inhalation, oral, mucosal absorption
- THC levels ~those by inhalation by oral & GI; first pass metabolism <10%
- THC lipophilic fat uptake; half-life~22 hr
- Distribution in fat variable, affected by cachexia?
- Hepatic metabolism: cytochrome p450; urinary clearance (range 2hrs-20 wks)
- GI absorption affected by GI function, mucosal absorption
- ↑ appetite/wght gain
 - Nelson K, Walsh D J Palliat Care 1994;10: 39-97;
 - Plasse TF, Gorter RW. Pharmacol Biochem Behav 1991;40:695-700.
- Evidence equivocal for use in cachexia-anorexia syndrome
 - Reuter SC, Martin JH. Clin Pharmacokinet 2016;55:807-12

Action of CB1 Receptor

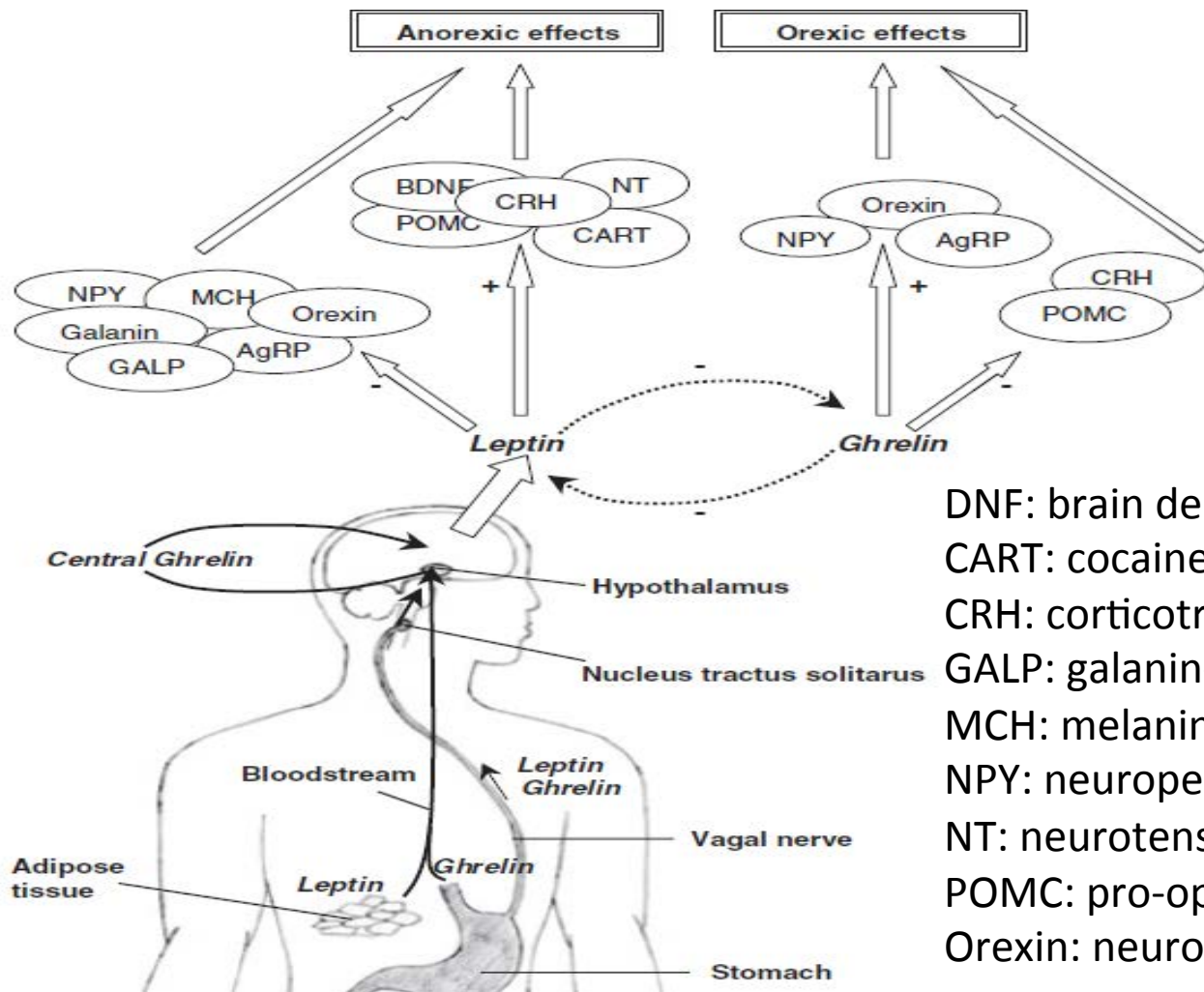




Ghrelin and Cannabinoids (1)

- Ghrelin: circulating brain & gut peptide
 - ↑ growth hormone secretion & appetite,
 - mediated by growth hormone receptor stimulation & AMPK (AMP activated kinase)
- CBDs: orexin (hypocretin) regulates arousal & appetite
- Ghrelin, Leptin & CBDs
 - ↑ AMPK hypothalamus
 - ↓ AMPK in liver & adipose tissue
 - suggesting AMPK stimulates appetite & ↑ peripheral effects of ghrelin & CBDs
- Intact ghrelin signaling needed for effects of CBDs on AMPK
 - Lim CT, Kola B, Feltrin D et al. Molec Cell Endocrinol 2013;365:303-8
 - Kola B, Wittman G, Bodnar I et al. FASEB J 2013;27:5112-21

Leptin/Ghrelin: Energy Balance



DNF: brain derived neurogenic factor

CART: cocaine-amphetamine regulated trans

CRH: corticotrophin releasing hormone

GALP: galanin-like peptide

MCH: melanin concentrating hormone

NPY: neuropeptide Y

NT: neurotensin

POMC: pro-opiomelatonin

Orexin: neuropeptide: alertness, appetite

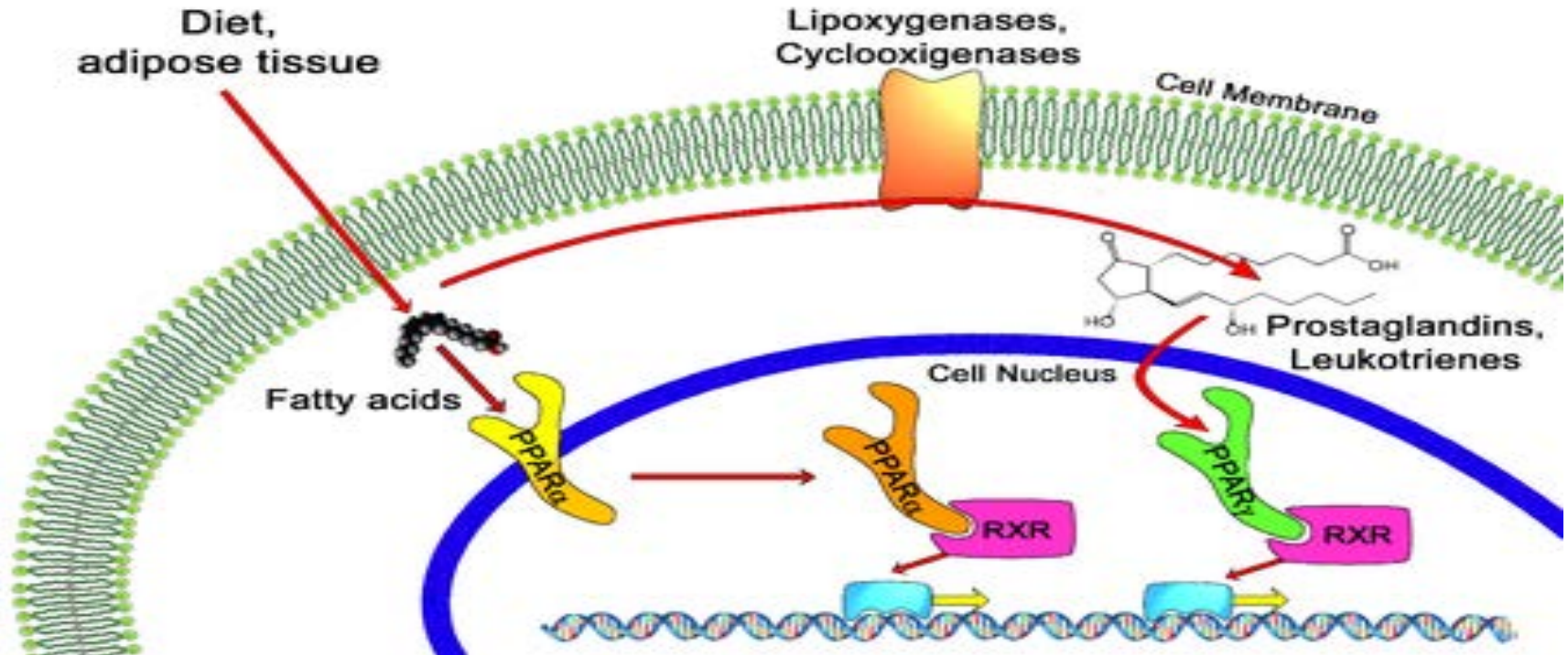
Cannabinoids and Taste

- Rat study: sweet/bitter, THC & CB1 antagonist (AM251)
 - THC ↑ sucrose hedonic response
 - ↓ rejection of quinine
 - ↑ palatability & intake of all foods
- AM251 reversed response to THC supporting action via CB1 receptor
Jarrett MM et al. Physiol Behavior 2007;90:425-30
- Blocking CB1 ↓ motivation to obtain food
- Highly palatable food stimulates dopamine (DA) in nucleus accumbens (NAc)
- effect on DA in taste rx to sucrose v aversive – quinine & NaCl
- THC ↑ sucrose effect & ↑ DA in NAc
- CB1 ↑ hedonic taste (sweet) but no effect on aversive taste
 - Droste SM, Saland Sk, Schlitter EK. Pharmacol Biochem Behav 2010;95:443-8
 - De Luca MA, Solinas M, Bimpisidis Z, et al. Neuropharmacology 2012;63:161-8

B-caryophyllene (BCP): Dietary phytocannabinoid

- BCP activate PPAR- α & - γ receptors & inhibit toll-like receptors
- \downarrow immune/inflammatory processes; synergy with μ -opioid receptor, antagonist nicotinic-acetylcholine receptors, no effect serotonergic/GABAergic receptors
- Effects: cardio-, nephro-protective, antioxidant, anti-inflammatory, antimicrobial, immune-modulator; nausea/vomiting; neuropathic pain
- Potential effect: neurologic function, neurodegenerative disease; taste; nausea/vomiting
- Oral bioavailability, lipophilic
 - Sharma C, Al Kaabi JM, Nurulain SM, et al. Curr Pharm Des 2016;22:3237-64

PPAR receptors



Neural effects Tetrahydrocannabivarin: Food reward/aversion

- Tetrahydrocannabivarin: CB1 antagonist
- 20 volunteers, fMRI, response to visual & taste stimuli (visual/taste chocolate & aversive response picture of moldy strawberries or strawberry taste)
- No difference in subjective ratings of taste (CB1 v placebo)
- fMRI ↑ response to chocolate & ↑ response to aversive stimuli
- CB1 antagonist ↑ neural response to + & - stimuli; potential for weight gain and weight loss
 - Tudge L, Williams C, Cowen PJ et al. Int J Neuropsychopharmacol 2014;18(6)
 - Tudge L, Williams C, Cowen PJ, McCabe C. Int J Neuropsychopharmacol 2015;

THC-induced taste avoidance in rat model

- THC aversive taste not mediated by κ -opioid receptor
- No effect on aversive taste seen in adults, minor inconsistent effect in adolescent rats
 - Flax SM, Wakeford AG, Cheng K et al. Psychopharmacology 2015;232:3193-201

THC & Cannabidiolic acid (CBDA): Acute anticipatory nausea

- Rat model; nausea & taste avoidance test
- THC ↓ conditioned taste avoidance, effect ↓ by CBDA
- Nausea ↓ by THC/CBDA independently & together; centrally mediated at the visceral insular cortex
- Suggested value as anti-nausea
 - Rock EM, Limebeer CL, Parker LA. Psychopharmacology 2015;232:4445-54
- No effect on aversive taste in adults, inconsistent effect in adolescent rats
- THC aversive taste not mediated by κ -opioid receptor

- Flax SM, Wakeford AG, Cheng K et al. Psychopharmacology 2015;232:3193-201

Cannabinoids and hedonic taste response

- Blocking CB1 ↓ motivation to obtain food
- Highly palatable food stimulates dopamine (DA) in nucleus accumbens (NAc)
- Assessed THC effect on DA on taste reactivity to sucrose v aversive – quinine & NaCl in rats
- THC ↑ sucrose effect & ↑ NAc DA
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 - De Luca MA, Solinas M, Bimpisidis Z, et al. Neuropharmacology 2012;63:161-8

Cannabinoids and Taste

- 57 adults, acute dose trial (3 days)
 - Saliva flow rate: – ve correlation with plasma drug level in single dose arm
 - Taste testing: no effect
 - But + self report of ↑taste response & ↑ hedonics
-
- Mattes RD, Shaw LM, Endelman K. Chem Senses 1994;19:125-40

THC palliates chemosensory change in cancer patients

- Pilot study: THC (2.5-10 mg v placebo BID) x 18 days (n=24/22); 21 completed study
- Taste/smell survey, 3 day food record, appetite, macronutrient preference, QOL questionnaire
- ↑chemosensory perception (p=0.026)
- food tasted better (p=0.04)
- ↑ appetite (p=0.05)
- ↑ calories as protein (p=0.008)
- ↑ quality of sleep & relaxation (p<0.05)
- ↑ QOL & total calorie intake THC & placebo

Cannabinoids Enhance Sweet Taste

- Cannabinoids act @ CB1 receptors in hypothalamus/limbic forebrain induce appetite & stimulate food intake
 - Endocannabinoids in plasma inverse to leptin
 - Taste peripheral target of leptin & cannabinoids
 - CB1 & T1r3 receptors on taste cells
 - Leptin ↓ sweet taste in mice
 - Cannabinoids ↑ sweet taste, no effect on salt, sour, bitter, umami
-
- Yoshida R, Ohkuri T, Jyotaki M, et al. Proc Natl Acad Sci USA 2010;107:935-9

Altered taste due to smoking substance

- 1250 opportunistically recruited (study 1)
 - 76 recruited abstainers, cannabis (recreational and daily users)
 - Taste assessed: Sweet, salt, sour, bitter, spicy
 - Multiple drug users & cannabis users ↑ preference for salt/sour
 - Daily cannabis & tobacco users ↑ preference for sweet, spicy
 - Past users of cannabis may have different responses to cannabinoids than prior nonusers
-
- Dovey TM, Boyland EJ, Trayner P et al. Appetite 2016;107:1-8



Cannabinoids and Taste

- Dronabinol (2.5 mg BID) alone or combined with megestrol (800 mg /d) v megestrol alone
- 469 pts with cancer related cachexia
- 49% reported ↑appetite with dronabinol
- No effect seen dronabinol or combination v megestrol
 - Jatoi A, Windschitl HE, Loprinzi CL et al. JCO 2002;20:567-73
- Dble blind study THC (2.5 mg) with/without CBD BID v placebo found no differences
- No effect due to dosing? ; individual titration may be needed
 - Strasser F, Luftner D, Possinger K et al. JCO 2006;24:3394-400

THC and taste

- 46 pts, advanced cancer; 21 completed study, 11 dronabinol (Marinol) [THC], 10 placebo, RX 18 days
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 - ↑ appreciation of food 73% v 30%
 - ↑ taste 55% v 10%
 - ↑ appetite $p < 0.05$, ↑ sleep quality,
 - no overall Δ QOL
- Brisbois T. Ann Oncol 2011
 - De Luca M Neuropharmacol 2012

Cannabis for Appetite Stimulation

- Survey 204 palliative care/cancer patients; 13% medicinal cannabis (n=26)
 - Of prior users: given for pain (n=9), appetite loss (n=9); psychological problems (n=5); insomnia (n=5), nausea (n=2)
 - Tablets/capsules preferred 71%, mouth spray 42%, vaporiser 41%
-
- Lockett T, Phillips J, Lintzeris N, et al. Intern Med J 2016;46:1269-75



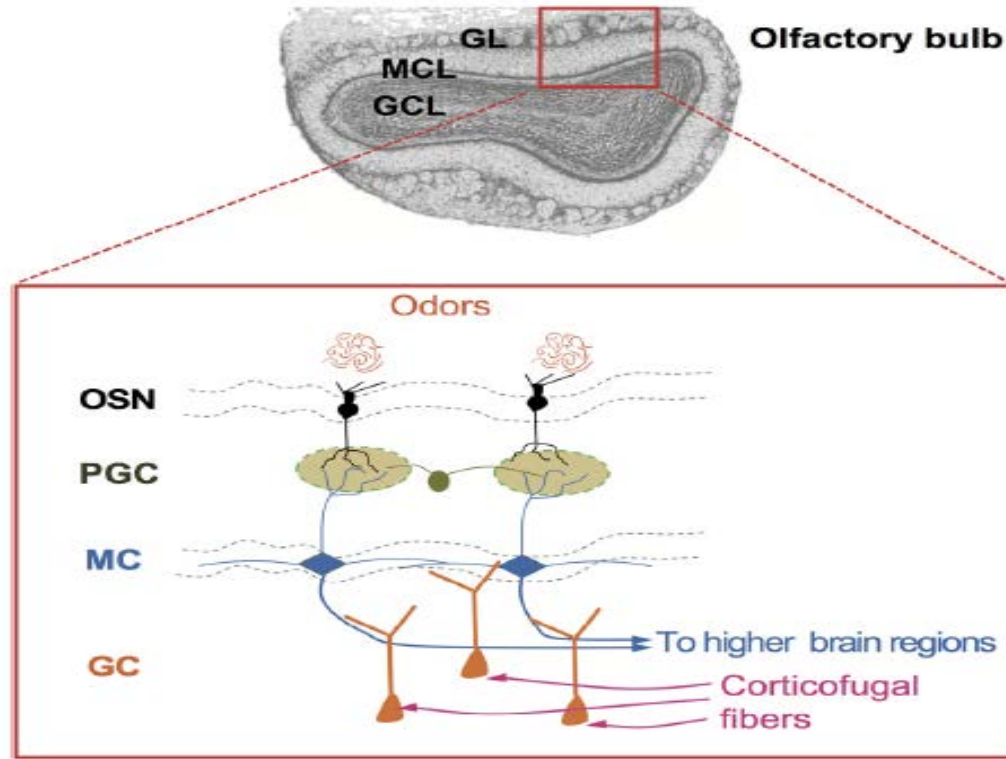
Macro-osmia



Cannabinoids and Olfaction

- THC approved in EU for AIDS-associated anorexia
- Addiction potential, incomplete understanding of mechanisms of activity
- Hunger ↑ sensory perception ~ ↑ food intake
- THC/CBD ↑ odor detection, ↑ food intake in mice
- CB1 receptors on cortical glutamatergic neurons project to the olfactory bulb in mice (role in humans unknown)
 - Soria-Gomez E, Bellocchio L. Nat Neurosci 2014;17:407-15

Olfactory Bulb

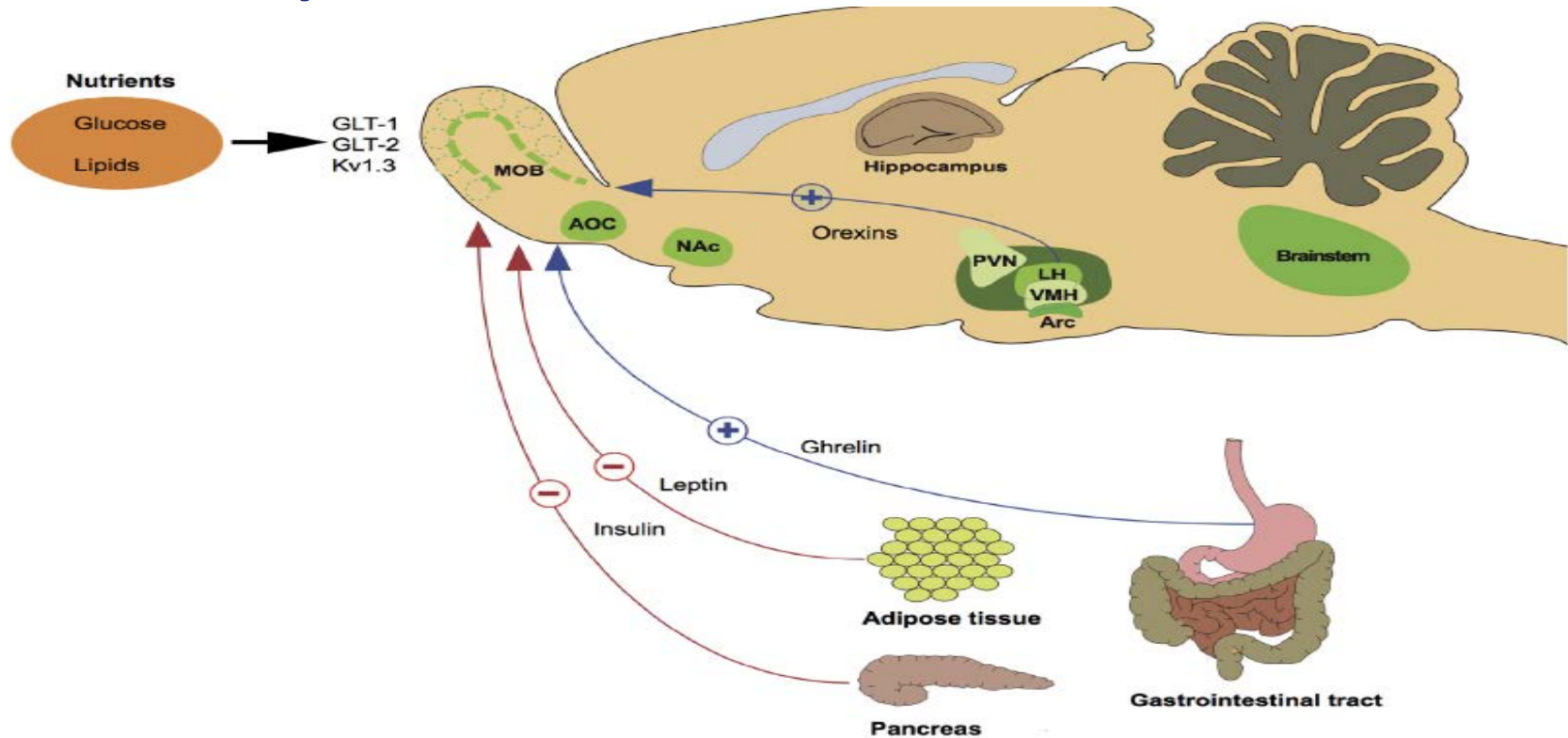


Olfactory bulb: MCL-mitral cell layer; GCL-granular cell layer

OSN-olfactory sensory neuron; MC-mitral cells

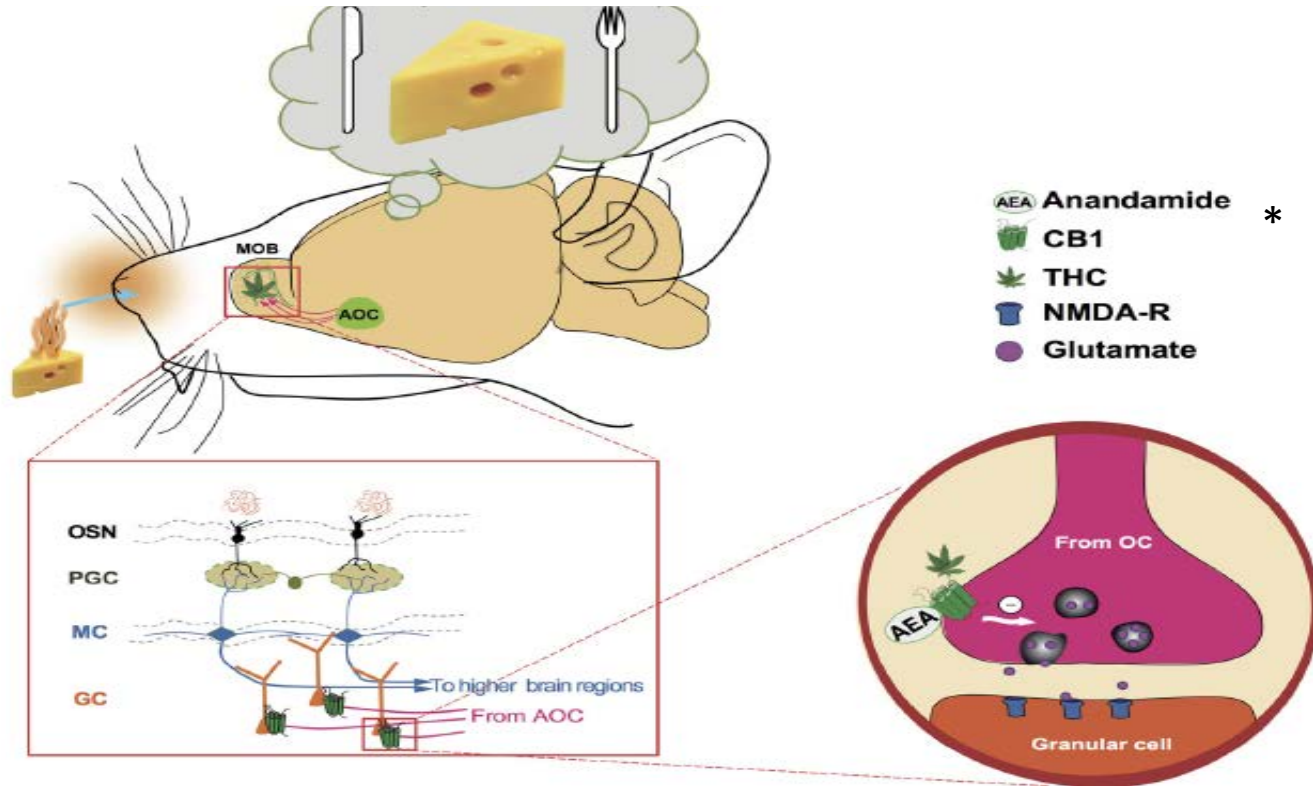
PCG (inhibitory) periglomerular cells; GC-(inhibitory) granular cell

Hormone/nutrient modulation of olfaction



GLT-glucose transporter; Kv1.3-voltage gated K channel; MOB-Main olfactory bulb; AOC-anterior olfactory cortex; PVN-paraventricular hypothalamus; LH-lateral hypothalamus; VMH-ventromedial hypothalamus; Arc-arcuate nucleus

Endocannabinoids* and Olfaction



Stimulation of olfactory perception & food intake. Presynaptic CB1 receptors.
CB1 stimulation ↓ glutaminergic receptors ↓ inhibition of olfaction

Impact of Analgesics on Olfactory Function

- 100 chronic pain pts; 95 healthy controls with no analgesics
- Olfactory testing (CN I) “Sniffin sticks” test, odor threshold & identification; intensity (VAS); CN V intranasal stimulation
- Chronic pain opioid & nonopioid (after control for neuropathy/chronic pain medication) significantly affect CN I, V sensory function
- Mechanism: via opioid receptors in CN V ganglion or CN I/V interaction
 - Mizera L, Gossrau G, Hummel T. Eur J Pain 2017;21:92-100

Therapy

Dietary counselling/modification

Seasoning, avoid unpleasant foods, extend dietary choice (pleasing color, form, smell, texture)

Peregrin J Am Diet Assoc 2006 106: 1536-40

Food preparation: spice/flavoring, increase umami flavor

Manage xerostomia

Manage oral disease

Zinc sulphate

Reduced severity & duration of taste dysfunction (18 patients)

Ripamonti et al, Cancer 1998 82: 1938-45

But benefit (NS) observed in larger study (169 patients; lower dose)

Halyard et al, Int Radiation Oncology Biol Phys 2007 67: 1318-22

Medications: clonazepam, gabapentin, megestrol, THC (Marinol), CBD

Thorne T, Olson K, Wismer W. JSCC 2015;23:284

Manage Oral/OPC pain and nausea if present

Taste Function in Oncology

- The mouth is a part of the body
- Critical role in diet/nutrition/sustenance and QOL
- Controlled treatment & prophylactic studies indicated with pharmaceutical product
- While receptors and mechanism of action are becoming better understood, many more questions than answers

Cannabinoids and Taste/flavor

- The mouth is a part of the body
- Critical role in diet/nutrition/sustenance and QOL
- Receptors & mechanism of action are becoming better understood, but, many more questions than answers
- Controlled treatment & prophylactic studies indicated with pharmaceutical product
- Improved control of patient variables needed
- Delivery, dose, route, schedule of cannabinoids to be determined
- Validated tools for oral condition, oral hygiene, dry mouth, taste, smell, PROs needed





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