PainWeek®

A Potpourri of Natural Opioids: Access, Safety, & Regulatory Responsibilities

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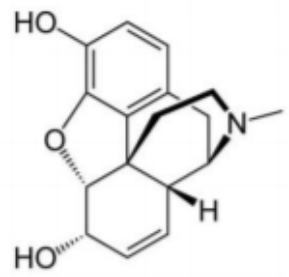
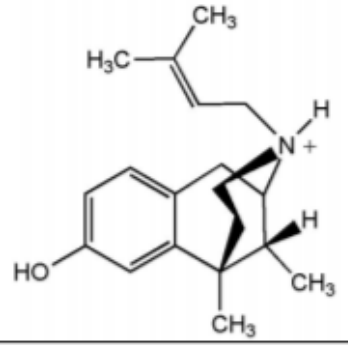
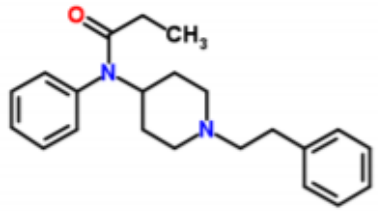
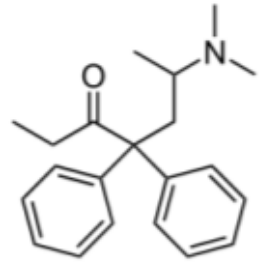
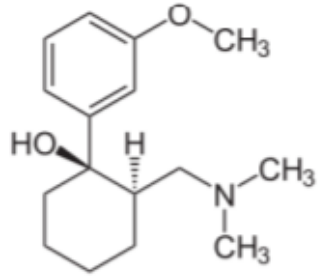
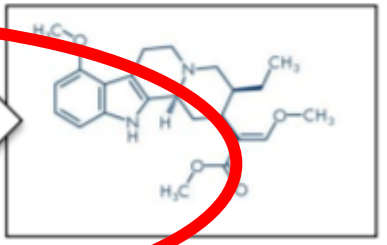
Disclosures

- Dr. Timothy Atkinson
  - Advisory Board, Epidemiology: Purdue Pharma LP
  - Consultant, axial Healthcare Inc
- Dr. Jeffrey Bettinger
  - Hisamitsu America, Inc: National Advisory Board
  - PainScript: Scientific Advisory Board
- Dr. Jessica Geiger
  - --Nothing to disclose

Objectives

- Describe the source and mechanisms of action for beta-casomorphine, collybolide, mitragyna speciosa alkaloids, and salvinorin A.
- Review risks, benefits, and potential drug interactions of the non-poppy derived naturally occurring opiate-like remedies.
- Discuss risk stratification and monitoring challenges associated with naturally occurring non-poppy derived opiate-like drugs.
- Determine potential place in therapy for each of the non-poppy derived opiate-like drug.

Whose Line Is It Anyway?

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Pentazocine	Alfentanil Fentanyl Remifentanil Sufentanil Meperidine Diphenoxylate[a] Loperamide[a] **Fentalogues** **Illicit Fentanyl Analogues** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil Others[b]	Methadone Propoxyphene **Mitragynine (Kratom)**	Tapentadol Tramadol 
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

Figure obtained from Dr. Jeff Fudin; Available from: https://paindr.com/wp-content/uploads/2020/11/Opioid-Structural-Classes-Figure_-updated-2020Nov.pdf

Different Types of Opioid Receptors

Opioid receptor	Intended effects when activated	Adverse effects when activated
μ-opioid receptors	• Analgesia • Anti-allodynia	• Respiratory depression • Euphoria/abuse liability • Peristalsis and reduced gastric secretions • Suppression of hypogonadal axis • Depression and anxiety • Nausea, vomiting • Tolerance/dependence
δ-opioid receptors	• Analgesia	• Respiratory depression • Peristalsis and reduced gastric secretions • Dependence • Rewarding
κ-opioid receptors	• Analgesia • Anti-allodynia	• Peristalsis and reduced gastric secretions • Depression, anxiety, increase suicidal tendencies • Dysphoria • Immunosuppression
ORL1	• Enhanced spinal analgesia • Anti-allodynia	• Reduction in opioid-rewarding effects • Reduction in potential for tolerance

Fudin J, Bettinger J, Cleary. Pharmacy Times. 2021.

“Everything’s Made Up and the Points Don’t Matter”

- Randomized Debate Format
- Audience determines who will take Pro vs Con position
- Debate
  - Pros and Cons will be discussed and arguments made
  - First presenter will have a chance to offer rebuttal
- Audience determines who wins each round

Mytragyna Species Alkaloids

Mytragyna Species

- Kratom (Thailand) or Biak-Biak (Malaysia)
  - Evergreen tree in the coffee family
  - Mitragynine (MG), 7α-hydroxyl-7H-mitragynine (7-OH-MG) and mitragynine pseudoindoxyl all have high affinity for opioid receptors.
- Potency
  - 7-OH-MG > morphine > MG
- 7-OH-MG and MG have high selectivity at the mu opioid receptor
- Structurally different from morphine

Raffa RB, Beckett JR, Brahmbhatt VN, et al. Orally active opioid compounds from a non-poppy source. J Med Chem. 2013;56:4840-4848.
Raffa RB, Pergolizzi JV, Taylor R, et a. Natures first “atypical opioids”:kratom and mitragynines. J Clin Pharm Ther. 2018;43:437-441.

DEBATE!

Pros of Mytragyna?

- Less emesis and respiratory depression than codeine
- High doses provide an opioid like effect
- Responds to naloxone
- 7-OH-MG is less constipating than morphine
- Helpful to mitigate opioid withdrawal
  - Less expensive than buprenorphine and does not require a prescription

Cons of Mytragyna?

- Abuse potential
- At low doses = cocaine like effect
- Antinociceptive tolerance develops to 7-OH-MG
- Widely available and not regulated
- Can cause tolerance
- Risk of seizures

Salvinorin A

The Kappa Opioid Receptor

- Kappa opioid receptors (KORs) are one of four opioid receptors found throughout body
  - Another G-protein coupled receptor
- Activation of KORs has shown to cause:
  - Antinociception1,2
  - Antipruritic effects3
  - Blockade of effects of psychostimulants3
- All without induction of physical dependence, respiratory depression, or inhibition of GI transit1,2
  - Has been shown to be implicated in relapse to drugs of abuse4

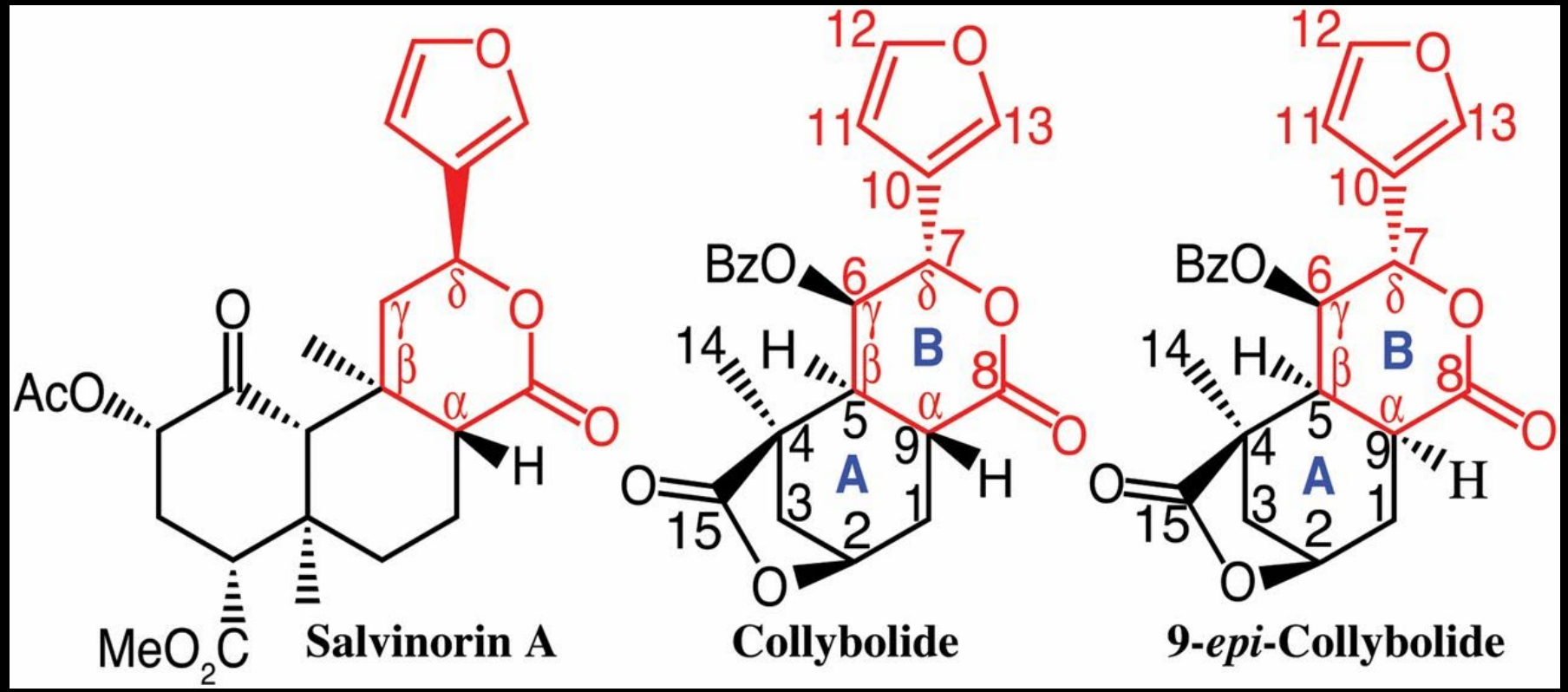
1. Pasternak GW. Multiple opiate receptors: [3H]ethylketocyclazocine receptor binding and ketocyclazocine analgesia. Proc Natl Acad Sci USA. 1980;77(6):3691–3694.
2. Tao YM, et al. LPK-26, a novel kappa-opioid receptor agonist with potent antinociceptive effects and low dependence potential. Eur J Pharmacol. 2008;584(2-3):306–311
3. Hang A, Wang YJ, He L, Liu JG. The role of the dynorphin/κ opioid receptor system in anxiety. Acta Pharmacol Sin. 2015;36(7):783–790.
4. Land BB, et al. Activation of the kappa opioid receptor in the dorsal raphe nucleus mediates the aversive effects of stress and reinstates drug seeking. Proc Natl Acad Sci USA. 2009;106(45):19168–19173.

Salvinorin A

- Non-nitrogenous diterpene
- Active metabolite of Mexican sage bush (Salvia divinorum).
  - Salvia divinorum is a recreational hallucinogen, brought to the US in the 1990's.
- Prepared by semi-synthetic modification of the natural product.
- Agonizes the kappa opioid receptor.
  - High selectivity
  - Not ionized at cellular pH
  - Highly lipophilic
    - Passes through blood brain barrier quickly

Raoch JJ, Shenvi RA. A Review of Salvinorin analogues and their kappa-opioid receptor activity. Bioorg Med Chem Lett. 2018; 28(9):1436-1445
Brito-da-Costa AM, Dias-da-Silva D, Gomes NGM. Pharmacokinetics and pharmacodynamics of salvinorin A and *Salvia divinorum:* Clinical and Forensic Aspects. Pharmaceuticals 2021;14:1-36.
Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: Salvia divinorum and kratom. Clin toicol. 2008;46:146-152.

Chemical Structures Sal A VS Collybolide



Gupta A, Gomes I, Bobeck EN, et al. Collybolide is a novel biased agonist of k-opioid receptors with potent antipruritic activity. Proc Natl Acad Sci USA. 2016;113(21): 6041-6046

DEBATE!

Pros of Salvinorin A?

- Fast on, fast off
- Inactive metabolites
- Interaction with the kappa receptor, mitigates some of the unwanted side effects of medications that interact with the mu receptor.
  - Specifically, respiratory depression
- Oral ingestion does not cause psychoactive effects
- Not detected in urine drug screens?
- Aversive effects

Cons of Salvinorin A?

- Can cause hallucinations
- CYP450 substrate = potential for drug interactions
- Might be legal…might not be, it depends on where you live
- Not detected on urine drug screens
- Minimal literature available

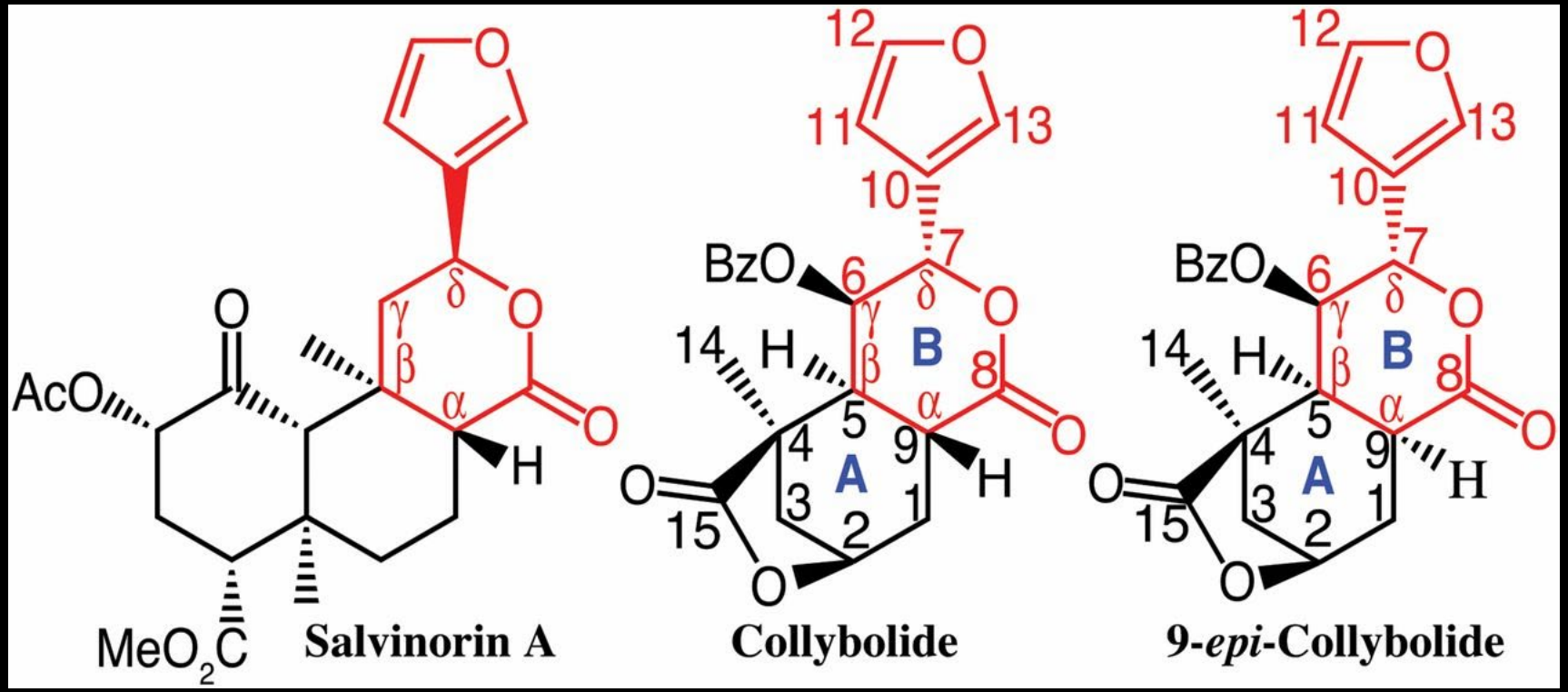
Collybolide

Collybolide

- A non-nitrogenous sesquiterpene derived from mushrooms in 1974
  - Collybia maculate
- Chemically has a furyl-delta-lactone core
  - Similar to that of Salvinorin A
- Has shown to be a highly potent and selective KOR agonist
- In vivo has shown to exhibit functional bias toward KOR activation
  - ~10-50 fold higher potency in activating mitogen-activated protein kinase pathways compared with Sal A
  - Equipotent for inhibiting adenylyl cyclase activity
  - ~10 fold higher potency in blocking non-histamine-mediated itch compared with Sal A

Gupta A, Gomes I, Bobeck EN, et al. Collybolide is a novel biased agonist of k-opioid receptors with potent antipruritic activity. Proc Natl Acad Sci USA. 2016;113(21): 6041-6046

Chemical Structures Sal A VS Colly



Gupta A, Gomes I, Bobeck EN, et al. Collybolide is a novel biased agonist of k-opioid receptors with potent antipruritic activity. Proc Natl Acad Sci USA. 2016;113(21): 6041-6046

DEBATE!

Pros of Collybolide?

- Biased agonistic ability and modifiable structure
  - Could represent a relatively ideal candidate for development of novel therapeutics targeting KOR
- Has been shown to exhibit antinociception in mice
- Has been shown to be aversive in mice
- Decreases immobility time in the forced swim test
  - May suggest that Colly may exhibit antidepressant activity
- Colly-mediated antipruitic effect seemed to be consistent and robust

Gupta A, Gomes I, Bobeck EN, et al. Collybolide is a novel biased agonist of k-opioid receptors with potent antipruritic activity. Proc Natl Acad Sci USA. 2016;113(21): 6041-6046

Cons of Collybolide?

- Appears to be poorly water-soluble
  - May create some barriers to get around in terms of drug development
- Still very preliminary data based on animal studies
- Antinociception is not directly associated with relief of chronic pain
- Has been suggested to be anxiogenic, as opposed to anxiolytic
- Unclear psychotropic effects
  - Sal A has shown to have potent psychotropic effects in humans

Gupta A, Gomes I, Bobeck EN, et al. Collybolide is a novel biased agonist of k-opioid receptors with potent antipruritic activity. Proc Natl Acad Sci USA. 2016;113(21): 6041-6046

Beta-Casamorphin

Opioid Peptides

- Several bioactive peptides that have shown opiate-like biological properties
- Typically around 4-8 amino acids long, has similar N-terminal sequence and bind with opioid receptors
- Can be produced by body itself (endogenous opioid peptides) or ingested via food and plant sources (exogenous opioid peptides)

Endogenous Opioid Peptides

- Endorphins
- Enkephalins
- Dynorphins
- Endomorphins

Exogenous Opioid Peptides

- Also known as exorphins
- Substances with opioid-like activity that are exogenously derived from outside food sources and various external or food-derived sources
- Key characteristics:
  - Produced in GI tract
  - Resist breakdown by intestinal enzymes (proteases)
  - Be absorbed in the bloodstream
  - Cross the blood-brain barrier to interact with central opioid receptors

Examples of Exorphins

Source	Parent Protein	Peptide Name
Bovine milk	Beta-casein	Beta-casomorphin-4 Beta-casomorphin-5 Beta-casomorphin-6 Beta-casomorphin-7
Bovine milk	Alpha-lactalbumin	Alpha-lactorphin
Human milk	Beta-casein	Beta-casomorphin-4 Beta-casomorphin-5 Beta-casomorphin-7 Beta-casomorphin-8
Human milk	Lactalbumin	Alpha-lactorphin
Soy	Beta-conglycinin	Soymorphin-5 Soymorphin-6 Soymorphin-7
Wheat	HMW Glutenin	Gluten exorphin A4 Gluten exorphin A5 Gluten exorphin B4 Gluten Exorphin B5

Tyagi A, Daliri EBW, Ofosu FK, et al. Food-derived opioid peptides in human health: A review. Int J Mol Sci. 2020;21:8825

Beta-Casomorphin

- An opioid peptide which is derived from digestion of beta-casein of milk (human, cow, buffalo)
  - Milk first discovered to have mu-opioid activity in 1979
- Also has been found in parmesan and cheddar cheese
- Several different peptides have been identified with varying intrinsic activities and binding affinities toward mu-opioid receptors

Henschen, A.; Brantl, V.; Teschemacher, H.; Lottspeich, F. β-Casomorphins–Novel Opioid Peptides Derived from Bovine Casein–Isolation and Structure. In Endogenous and Exogenous Opiate Agonists and Antagonists; Elsevier: Amsterdam, The Netherlands, 1980; pp. 233–236.

Opioid Activity of Beta-Casomorphins

Opioid Peptide	Amino Acid Sequence	Opioid Activity (IC50, uM: Guinea-Pig Ileum (mu)	Opioid Activity (IC50, uM): Mouse vas Deferens (delta)
Bovine Beta-casomorphin-4[2]	Tyr-Pro-Phe-Pro	22	84
Bovine Beta-casomorphin-5[2]	Tyr-Pro-Phe-Pro-Gly	6.5	40
Bovine Beta-casomorphin-6[2]	Tyr-Pro-Phe-Pro-Gly-Pro	27.4	>150
Bovine Beta-casomorphin-7[2]	Tyr-Pro-Phe-Pro-Gly-Pro-Ile	57	>200
Human Beta-casomorphin-4[3]	Tyr-Pro-Phe-Val	19	750
Human Beta-casomorphin-5[3]	Tyr-Pro-Phe-Val-Glu	14	N/a
Human Beta-casomorphin-7[3]	Tyr-Pro-Phe-Val-Glu-Pro-Ile	25	350
Human Beta-casomorphin-8[3]	Tyr-Pro-Phe-Val-Glu-Pro-Ile-Pro	25	540

1. Tyagi A, Daliri EBW, Ofosu FK, et al. Food-derived opioid peptides in human health: A review. Int J Mol Sci. 2020;21:8825
2. Brantl V, Teschemacher H, Blasig J, et al. Opioid activities of Beta-casomorphins. Life Sci. 1981;28:1903-1909.
3. Koch G, Widemann K, Teschemacher H. Opioid activities of human Beta-casomorphins. Naunyn-Schmiedeberg Arch Pharmacol. 1985;331:351-354

DEBATE!

Pros of Beta-Casomorphin?

- Promotes analgesia1,2
- Performs anti-diarrheal action by enhancing net water and electrolyte absorption in the small and large intestine3
  - Can prolong GI transit time3
- Potential antihypertensive activity4
- Positive anti-arrhythmic effect, thus can have a cardioprotective function3
- Can cause sleepiness (has actually been studied in babies)3,5

1. Matthies, H.; Stark, H.; Hartrodt, B.; Ruethrich, H.-L.; Spieler, H.-T.; Barth, A.; Neubert, K. Derivatives of β-casomorphins with high analgesic potency. Peptides 1984, 5, 463–470
2. Grecksch, G.; Schweigert, C.; Matthies, H. Evidence for analgesic activity ofβ-casomorphin in rats.Neurosci. Lett. 1981, 27, 325–328.
3. Tyagi A, Daliri EBW, Ofosu FK, et al. Food-derived opioid peptides in human health: A review. Int J Mol Sci. 2020;21:8825
4. Jauhiainen T, Korpela. Milk peptides and blood pressure. J Nutr. 2007;137(3 Supppl 2):825S-9S.
5. Calvo, C.F.; Cesselin, F.; Gelman, M.; Glowinski, J. Identification of an opioid peptide secreted by rat embryonic mixed brain cells as a promoter of macrophage migration. Eur. J. Neurosci. 2000, 12, 2676–2684.

Even More Pros??

- Believed to modulate release of prolactin and oxytocin during lactation1
- Can play a role in insulin and somatostatin secretion2
- Interacts with opiate receptors on the serosal side of intestinal epithelium playing important role in electrolyte transfer and food intake3
- Can provide some immunity, suppressing and stimulating lymphocyte proliferation depending on concentration1
- Improvements in memory and learning in mice models4

1. Tyagi A, Daliri EBW, Ofosu FK, et al. Food-derived opioid peptides in human health: A review. Int J Mol Sci. 2020;21:8825
2. Gobbetti M, Stepaniak L, De Angelis M, Corsetti A, Di Cagno R (2002) Latent bioactive peptides in milk proteins: proteolytic activation and significance in dairy processing. Crit Rev Food Sci Nutr 42(3):223–239
3. Lin, L.; Umahara, M.; York, D.; Bray, G. β-Casomorphins stimulate and enterostatin inhibits the intake of dietary fat in rats. Peptides 1998, 19, 325–331
4. Sakaguchi, M.; Koseki, M.; Wakamatsu, M.; Matsumura, E. Effects of systemic administration of β-casomorphin-5 on learning and memory in mice. Eur. J. Pharmacol. 2006, 530, 81–87

Cons of Beta-Casomorphin?

- First, really has been minimally studied, especially in actual controlled trials
- Have shown depressive effects on the central respiratory system, causing a slowing of respiratory frequency and tidal volume1
- Could be a risk factor for human ischemic heart disease, atherosclerosis, type I diabetes, and sudden death syndrome2,3
- May be related to apnea in sudden infant death syndrome; a positive relationship has been reported4

1. Rutherfurd-Markwick KJ (2012) Food proteins as a source of bioactive peptides with diverse functions. Br J Nutr 108(2):149–157
2. Tailford KA, Berry CL, Thomas AC, Campbell JH (2003) A casein variant in cow's milk is atherogenic. Atherosclerosis 170(1):13–19
3. Kamiński S, Cieślińska A, Kostyra E (2007) Polymorphism of bovine beta-casein and its potential effect on human health. J Appl Genet 48(3):189–198
4. Bell SJ, Grochoski GT, Clarke AJ (2006) Health implications of milk containing β-casein with the A2 genetic variant. Crit Rev Food Sci Nutr 46(1):93–100

Questions?

Thank you!