PEA: Beyond Pain Management

Presented by
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What we will be covering today:

- What is PEA?
- PEA Synthesis
- PEA Pathways
- PEA & The Central Nervous System
- Endocannabinoid System
- The Stress Response
- PEA in Practice
- Summary

What is PEA?

- Palmitoylethanolamide (PEA)
  - An endocannabinoid (eCB)-like bioactive lipid mediator belonging to the N-acyl-ethanolamine (NAE) fatty acid amide family
  - Synthesized on demand within the lipid bilayer
  - Suggested as a pro-homeostatic protective response to cellular injury
  - Research indicates it is up-regulated in disease states
  - Its pleiotropic effects include:
    - anti-inflammatory, analgesic, anticonvulsant, antimicrobial, antipyretic, antiepileptic, immunomodulatory and neuroprotective activities

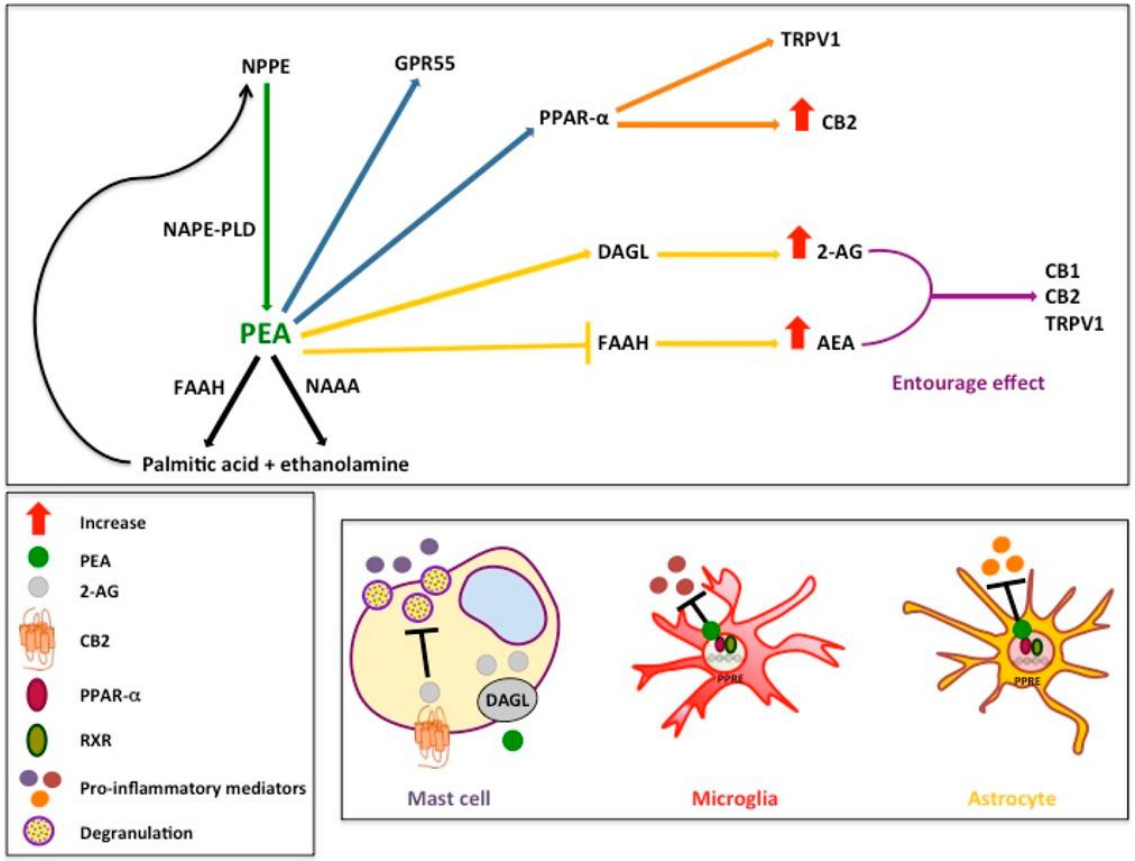
Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.

Multiple Pathways for PEA

- Multiple mechanisms of action:
  - Predominantly targeting the nuclear receptor peroxisome proliferator-activated alpha (PPAR-α)
    - Reduces the release of proinflammatory cytokines (e.g. TNF-α and IL-1β).
    - Regulates mast cell activity within the CNS & peripheral nervous system.
  - Directly binding to cannabinoid receptors G protein-coupled receptor 55 (GPR55) & G protein-coupled receptor 119 (GPR119).
  - Indirectly activating cannabinoid receptors 1 and 2 (CB1 and CB2) by inhibiting the breakdown of the endocannabinoid, anandamide (AEA) leading to the ‘Entourage Effect’.

Clayton, P., Hill, M., Bogoda, N., Subah, S. & Venkatesh, R. Palmitoylethanolamide: A Natural Compound for Health Management. Int J Mol Sci 22, 5305 (2021).

Multiple Pathways for PEA



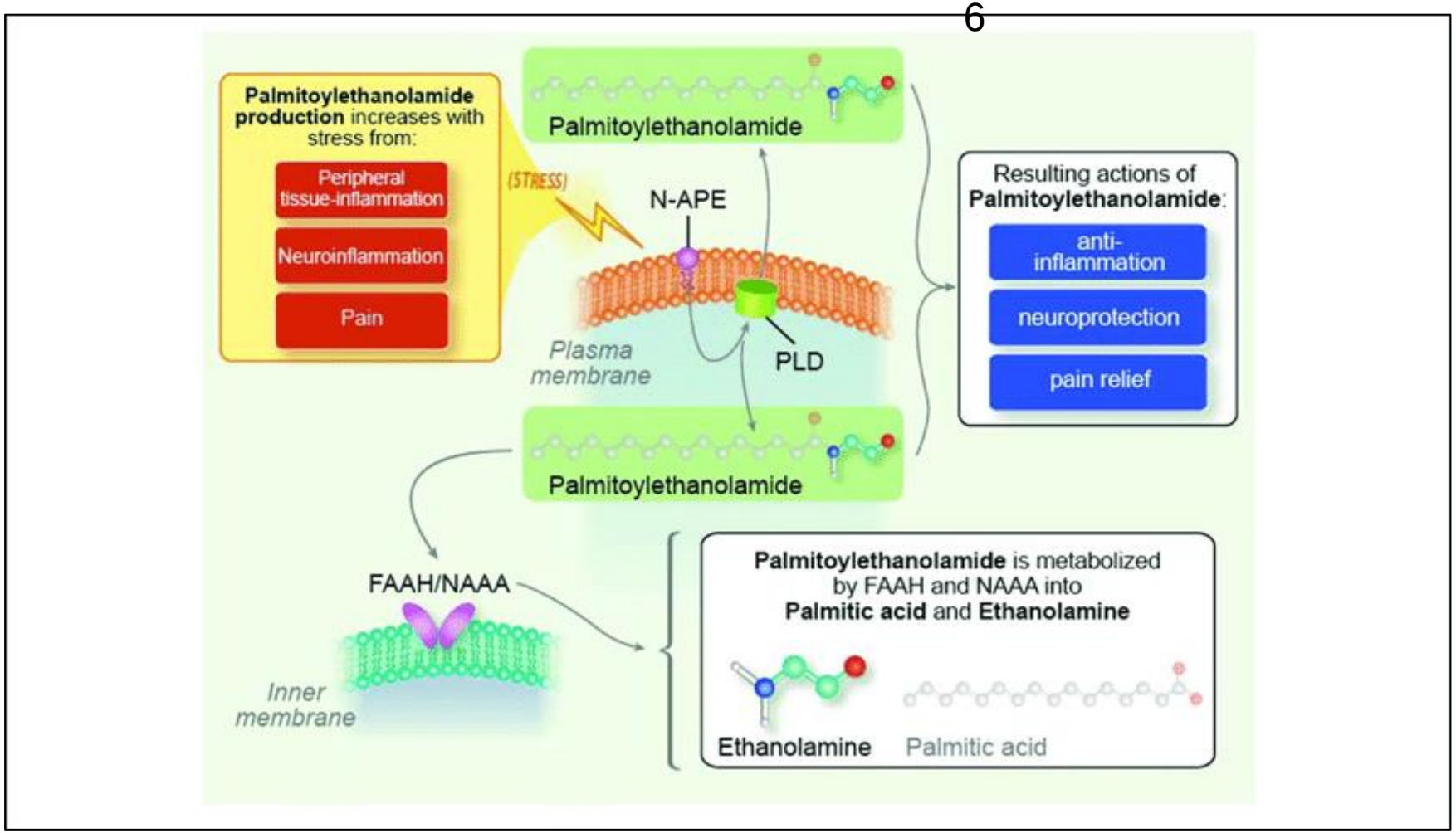
Abbreviations:

- 2-AG: 2-arachidonoylglycerol
- AEA: anandamide
- CB1: type-1 cannabinoid receptors
- CB2: type-2 cannabinoid receptors
- DAGL: diacylglycerol lipase
- FAAH: fatty acid amide hydrolase
- GPR55: G-protein coupled receptor 55
- NAAA: N-acylethanolamide hydrolyzing acid amidase
- NAPE-PLD: N-acyl-phosphatidyl-ethanolamine-selective phospholipase D
- **PEA: palmitoylethanolamide**
- PPAR-α: peroxisome proliferator-activated receptor-α
- TRPV1: transient receptor potential vanilloid type-1

Petrosino S, Moriello AS. Palmitoylethanolamide: A Nutritional Approach to Keep Neuroinflammation within Physiological Boundaries—A Systematic Review. Int J Mol Sci. 2020;21(24):9526. doi:10.3390/ijms21249526

PEA Synthesis

- Endogenous PEA is generally insufficient to counter chronic allostatic load as seen in chronic inflammatory disorders.
- Research indicates external use of PEA aids the return to homoeostasis.



Skaper, S. D., Facci, L., Zusso, M. & Giusti, P. An Inflammation-Centric View of Neurological Disease: Beyond the Neuron. *Front Cell Neurosci* **12**, 72 (2018).

PEA & Central Nervous System

- Neuro-inflammation & microglial activation amplifies the breakdown of PEA, reducing its availability in the CNS.
- Research has shown stimulating PEA availability through supplementation supports endogenous production.
- Reduced expression of PPAR-α in inflammatory conditions is reversed with PEA supplementation in studies.

Muccioli GG, Stella N. Microglia produce and hydrolyze palmitoylethanolamide. Neuropharmacology. 2008;54(1):16–22. doi: 10.1016/j.neuropharm.2007.05.015,

Guasti L, Richardson D, Jhaveri M, Eldeeb K, Barrett D, Elphick MR, et al. Minocycline treatment inhibits microglial activation and alters spinal levels of endocannabinoids in a rat model of neuropathic pain. Mol Pain. 2009;5(1):35–35. doi: 10.1186/1744-8069-5-35 .

Petrosino S, Schiano Moriello A, Cerrato S, Fusco M, Puigdemont A, De Petrocellis L, et al. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. Br J Pharmacol. 2016 Apr;173(7):1154-62. doi: 10.1111/bph.13084 .

PEA & Central Nervous System

- Suggested PEA can enhance neurogenesis and synaptic plasticity leading to improved memory and decision making.
- Possibly assisting an individual implement behaviour change to develop greater resilience.
- As all human studies to date report PEA to be well tolerated and without adverse effects the potential role of PEA in enhancing mental health.
- Via the entourage effect, PEA may support the sleep–wake balance in healthy adults.

Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A Natural Compound for Health Management. Int J Mol Sci. 2021;22(10):5305. doi:10.3390/ijms22105305

Endocannabinoid System

- Functions as a pleiotropic signalling system – Discovered in the late 1980s.
- Promotes homeostasis
- Using a complex array of messenger molecules:
  - Receptor sites
  - Enzymes

Grotenhermen F. Cannabinoids and the endocannabinoid system. Cannabinoids. 2006;1(1):10-4.
Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.

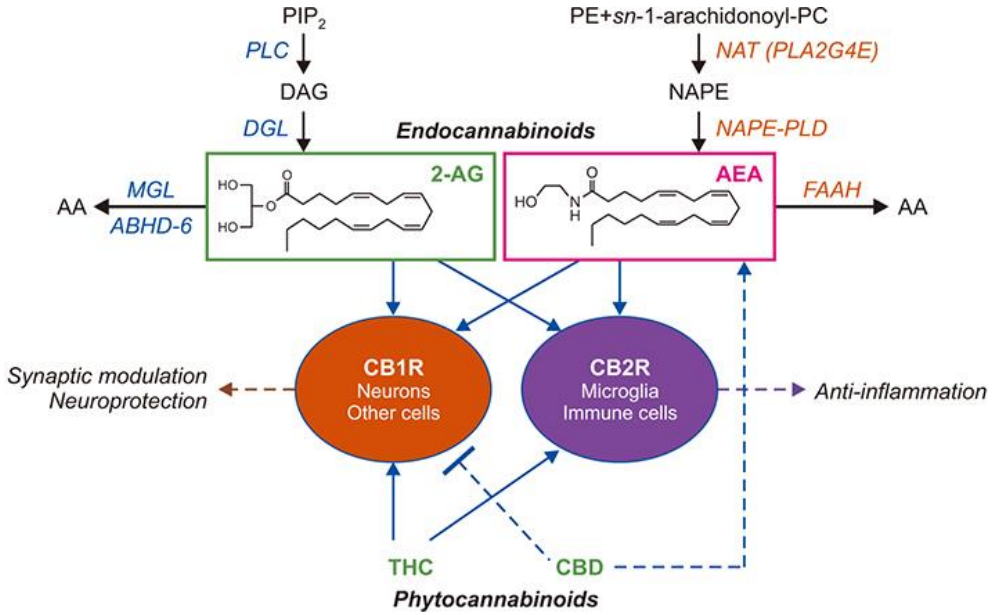
Endocannabinoid System

- Affects:
  - Hippocampal neurogenesis: memory
  - Homeostasis of energy balance and metabolism
  - Regulation of the HPA axis
    - Stress response & emotion regulation.
  - Production of other neurotransmitters as required.

Grotenhermen F. Cannabinoids and the endocannabinoid system. Cannabinoids. 2006;1(1):10-4.
Barrie N, Manolios N. The endocannabinoid system in pain and inflammation: its relevance to rheumatic disease. Eur J Rheumatol. 2017 Sep;4(3):210-218. doi:10.5152/eurjrheum.2017.17025.

Endocannabinoid System (ECS) & Stress

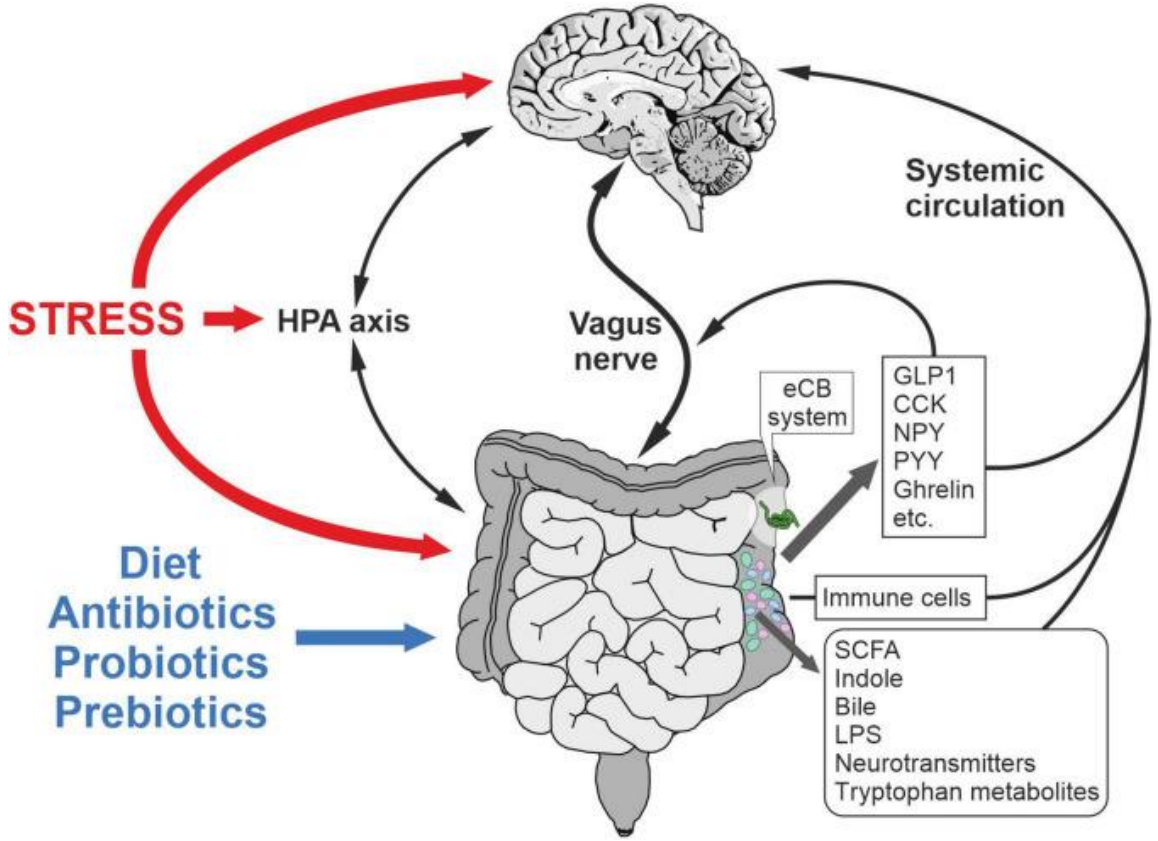
- ECS affects: HPA axis, memory & sleep regulation
- An association between a low intake of omega-3 fatty acids & poor endocannabinoid function has been established.



Lafourcade, M., Larrieu, T., Mato, S., Duffaud, A., Sepers, M., Matias, I., De Smedt-Peyrusse, V., Labrousse, V. F., Bretillon, L., Matute, C., Rodríguez-Puertas, R., Layé, S., & Manzoni, O. J. (2011). Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. Nature neuroscience, 14(3), 345–350. https://doi.org/10.1038/nn.2736

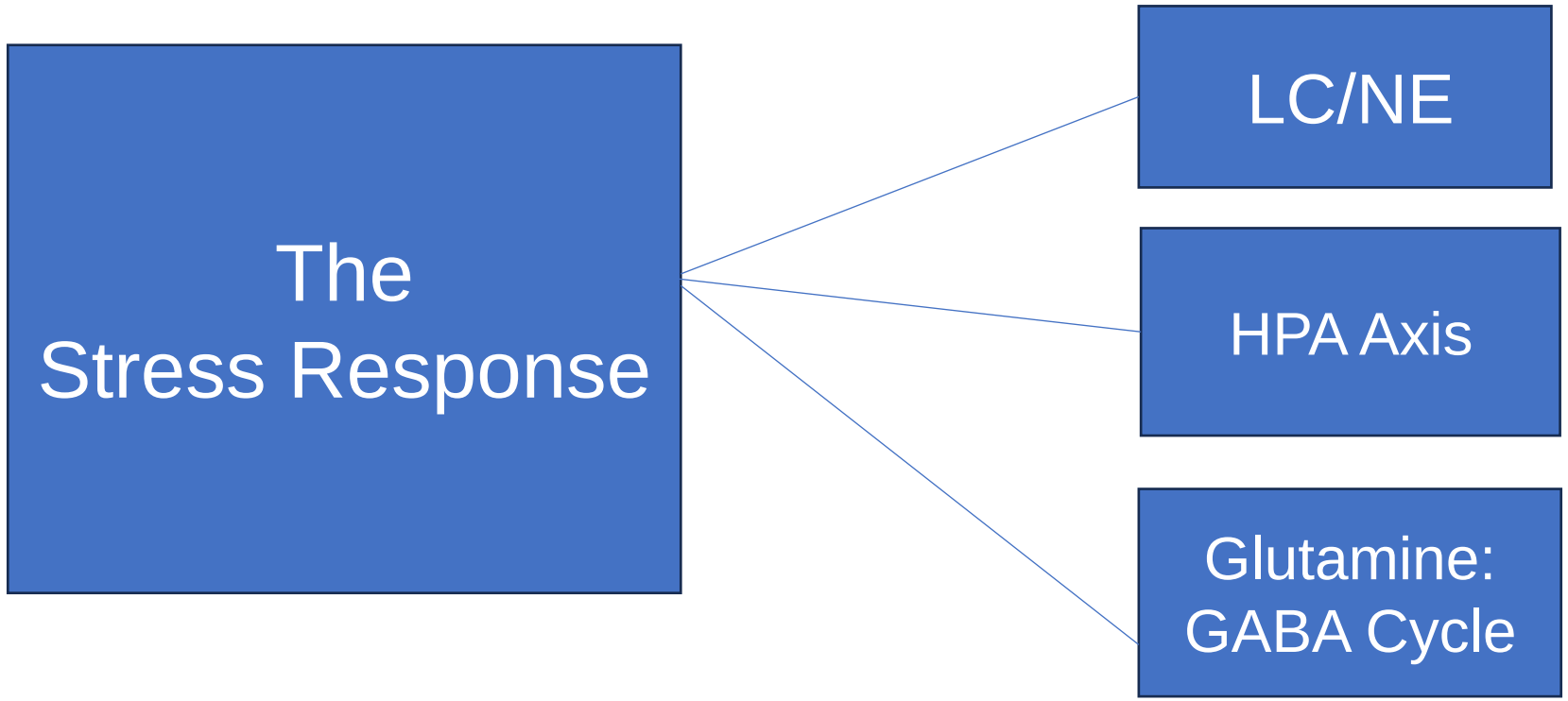
Lim J, Squire E, Jung KM. Phytocannabinoids, the Endocannabinoid System and Male Reproduction. World J Mens Health. 2023 Jan;41(1):1-10. https://doi.org/10.5534/wjmh.220132

Endocannabinoid System (ECS) & Stress

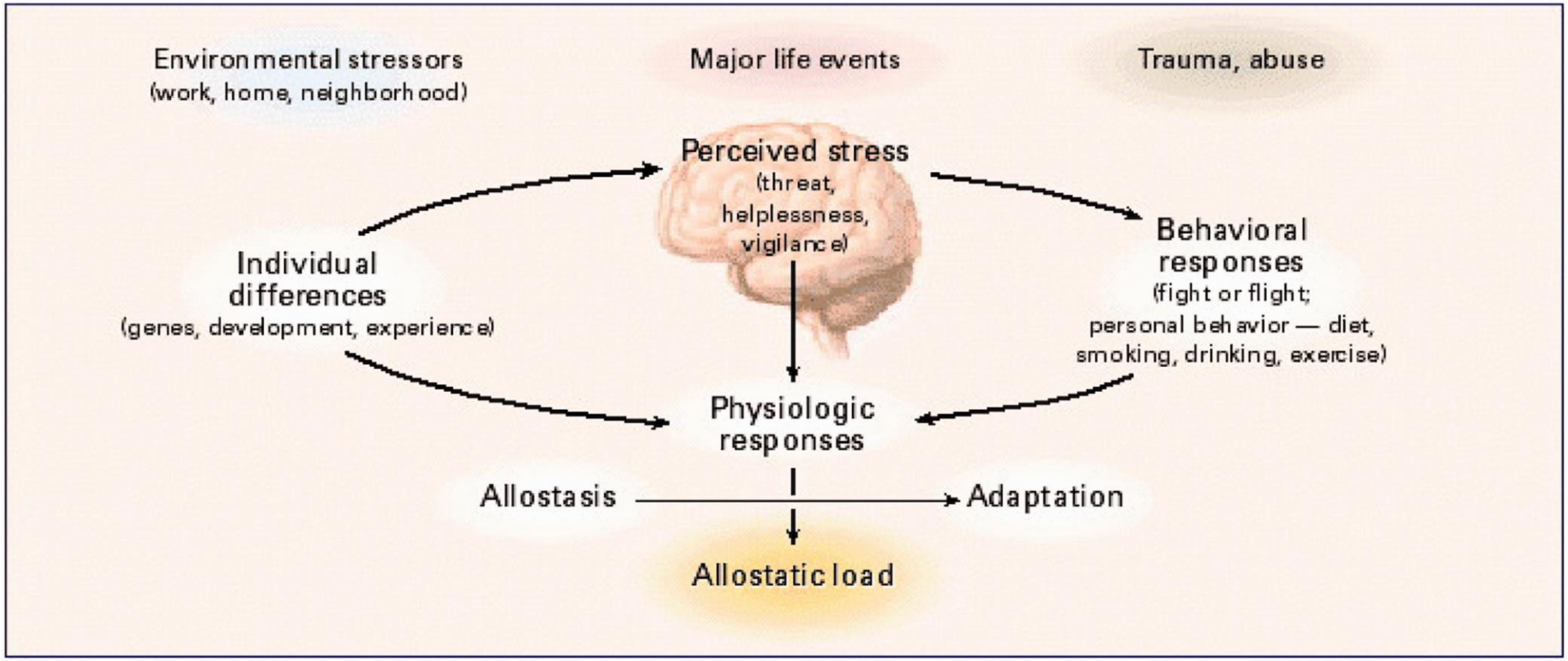


Srivastava RK, Lutz B, Ruiz de Azua I. The Microbiome and Gut Endocannabinoid System in the Regulation of Stress Responses and Metabolism. Front Cell Neurosci. 2022;16:867267. Published 2022 May 11. doi:10.3389/fncel.2022.867267

Key Features of the Stress Response



The Stress Response Factors



McEwen BS. Neurobiological and Systemic Effects of Chronic Stress. Chronic Stress. 2017;1:2470547017692328. doi:10.1177/2470547017692328

The Stress Response

- Noradrenergic neurons of the Locus caeruleas/Norepinephrine System(LC/NE) in the brain are predominantly responsible for the immediate ‘fight or flight response
- Activation of the hypothalamic-pituitary adrenal (HPA) axis & sympathetic nervous system (SNS)
- Chronic, acute or severe stress decreases glutamate/GABA cycling: leading to neuronal hyperexcitation

Meyerhoff DJ, Mon A, Metzler T, Neylan TC. Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality. Sleep. 2014;37(5):893-900. Published 2014 May 1. doi:10.5665/sleep.3654

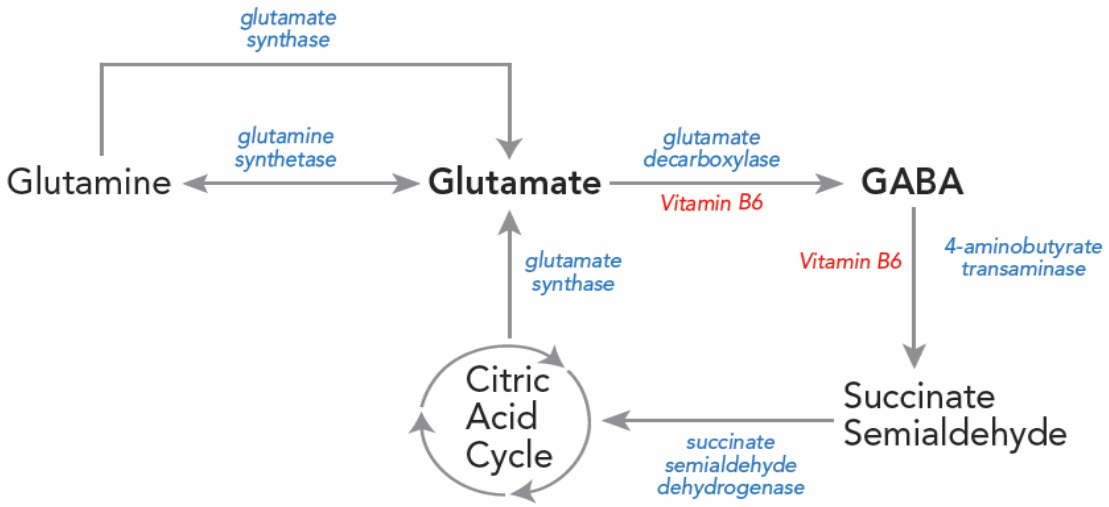
Gold PW. The organization of the stress system and its dysregulation in depressive illness. *Molecular Psychiatry*. 2014;20(1):32-47. doi:10.1038/mp.2014.163

The Stress Response

- Chronic stress leads to:
  - Excess cortisol from persistent hypothalamic-pituitary-adrenal (HPA) axis activation
  - Cortisol binds to receptors in the hippocampus, the area of the brain responsible for memory, learning and emotions
  - Cortisol levels can change a person's perception of stress.
  - Inflammatory changes in the CNS lead to mood disturbance.

Meyerhoff DJ, Mon A, Metzler T, Neylan TC. Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality. Sleep. 2014;37(5):893-900. Published 2014 May 1. doi:10.5665/sleep.3654

The Stress Response



Glutamate & GABA Cycling

- Dysregulated glutamate/GABA cycling predisposes individuals to stress, anxiety, depression and sleep dysregulation.
- Alters optimal cortical activity: sensation, perception, memory, association, thought, and voluntary physical action.

Jie F, Yin G, Yang W, et al. Stress in Regulation of GABA Amygdala System and Relevance to Neuropsychiatric Diseases. Frontiers in Neuroscience. 2018 ;12:562. DOI: 10.3389/fnins.2018.00562. PMID: 30154693; PMCID: PMC6103381.

Wordpress.com. Published 2024. Accessed May 20, 2024. https://neuroendoimmune.wordpress.com/wp-content/uploads/2013/07/gaba-glutamate-synthesis.png

The Stress Response

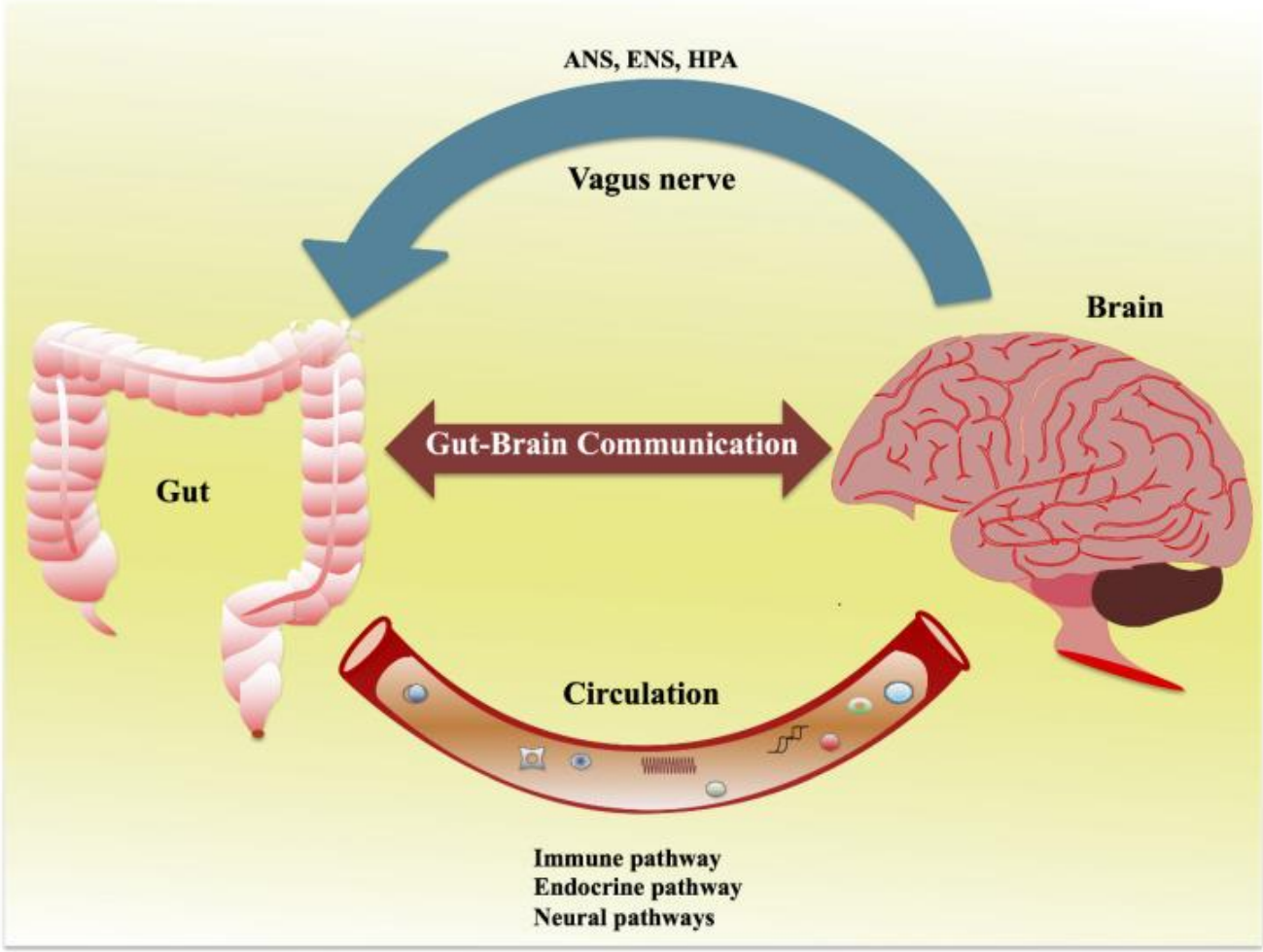
- Stressful situations can change the neural architecture
  - Reduced neuron density
  - Changes the pre-cortex & hippocampus
- Reducing a person's ability to manage stress.
- Extended stressful situations stimulate the release of glutamate & noradrenaline

Musazzi L, Treccani G, Popoli M. Functional and structural remodeling of glutamate synapses in prefrontal and frontal cortex induced by behavioral stress. *Front Psychiatry*. 2015;6:60. Published 2015 Apr 27. doi:10.3389/fpsyt.2015.00060,

Gold PW. The organization of the stress system and its dysregulation in depressive illness. *Molecular Psychiatry*. 2014;20(1):32-47. doi:10.1038/mp.2014.163

The Stress Response

- Greater understanding of the interconnection within the body.
- Involving inflammation, neurotransmitters, ecosystems and receptors.



Kanmani Suganya, Koo BS. Gut–Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. International journal of molecular sciences. 2020;21(20):7551-7551. doi:https://doi.org/10.3390/ijms21207551

The Stress response

- Neuro Inflammation is crucial many cognitive, behavioural, the stress response and mood disorders.
- Neuroinflammatory cascades damage neuronal structures, impair neuronal function and viability.
- Endocannabinoids & N-acyl-ethanolamine play a role in the regulation of behaviour, mood and cognition.
- Levels are dysregulated in many mental health conditions and dysfunctions.

Zimmermann T, Bartsch JC, Beer A, et al. Impaired anandamide/palmitoylethanolamide signaling in hippocampal glutamatergic neurons alters synaptic plasticity, learning, and emotional responses. *Neuropsychopharmacology*. 2019;44(8):1377-1388. doi:10.1038/s41386-018-0274-7

The Stress Response: Anandamide(AEA)

- AEA is a byproduct of PEA metabolism
  - A reduction in AEA is suggested to amplify the stress responses & activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to an increase in anxiety behaviour
  - High levels of AEA are linked to wakefulness in healthy individuals.
  - Declining levels in the elderly are linked with circadian rhythm imbalance and cognitive impairment.

Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A Natural Compound for Health Management. Int J Mol Sci. 2021;22(10):5305. doi:10.3390/ijms22105305

PEA in Practice

- Lipid soluble structure
- PEA has poor water solubility
- Reducing its absorption & bioavailability
- Micronisation of PEA improved bioavailability in animal studies.
- Numerous studies highlight its ability to be used with other therapeutic items.

Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020,
Beggiato S, Tomasini MC, Ferraro L. Palmitoylethanolamide (PEA) as a potential therapeutic agent in Alzheimer's disease. Front Pharmacol. 2019 Jul 24;10:821. doi: 10.3389/fphar.2019.00821.

PEA in Practice

- Clinically relevant dosages - 300mg/day to 2,400mg/day depending on the condition.
- Additional cofactors which support metabolism of PEA may apply the intervention.
- Lipid soluble items may take up six weeks to be fully optimal.

Gabrielsson L, Mattsson S, Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. Br J Clin Pharmacol. 2016 Oct;82(4):932-42. doi: 10.1111/bcp.13020.

Summary

- The stress response has many facets which makes PEA a suitable tool.
- The stress response affects the immune system, central nervous system, endocannabinoid system & may drive inflammation.
- PEA has robust evidence to support these systems.