PsychoEndocrinology: The Role of Thyrotropin Releasing Hormone (TRH) in Anxiety and Depression

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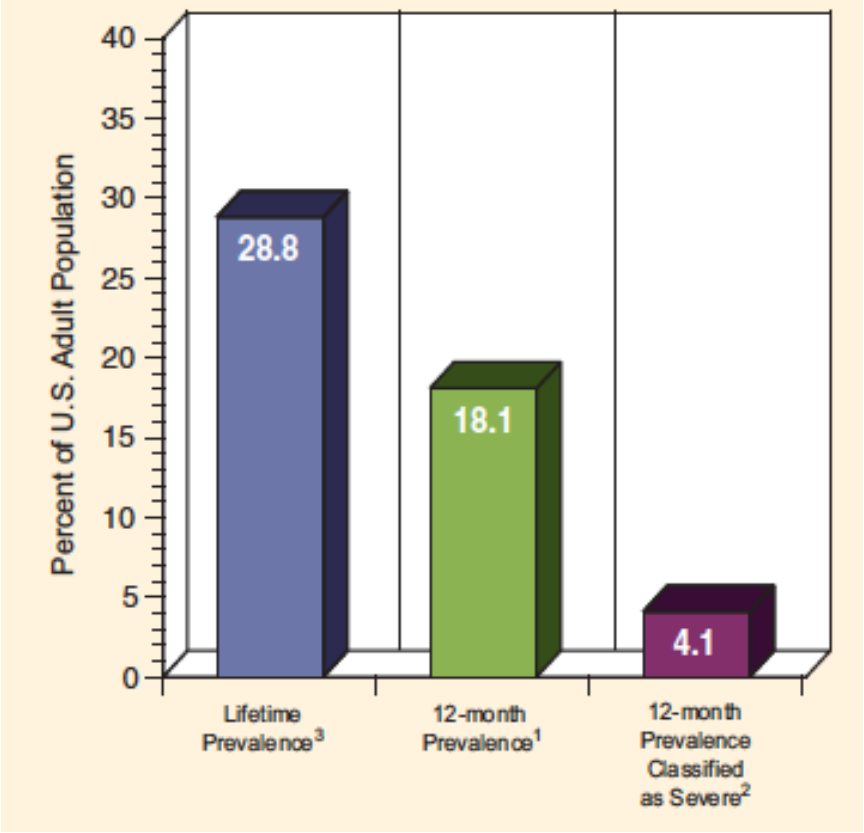
Goals

- Review the scope of anxiety
- Understand role of hormone TRH
  - Anxiety
  - Depression physiology
- Learn exam, historical findings related to TRH
- Understand clinical applications to treatment

INTRODUCTION

Prevalence of Anxiety

- Lifetime: 28.8%[1]
- 12-month: 18%[1]
- Reported onset: 4-11 years[1,2]
- Chronic course[3]



1. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry.* 2005;62(6):617-627.
2. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: a review of recent literature. *Current opinion in psychiatry.* 2007;20(4):359-364.
3. Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychological medicine.* 2013;43(5):897-910.

Efficacy of Treatment

- 30% fail to respond (Benzo's)[7]
- Weaning failure rate 85%[8]
- Treatment and post[9]
  - Cognitive decline, impaired productivity
  - Persists up to 3 yrs post discontinuation

7. Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *Journal of clinical pharmacy and therapeutics.* 2001;26(5):363-367.
8. Vicens C, Bejarano F, Sempere E, et al. Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care. *The British journal of psychiatry : the journal of mental science.* 2014;204(6):471-479.
9. Stewart SA. The effects of benzodiazepines on cognition. *The Journal of clinical psychiatry.* 2005;66 Suppl 2:9-13.

"It has become apparent that in the solution of these problems psychiatry will be brought to medicine and medicine will come to psychiatry."

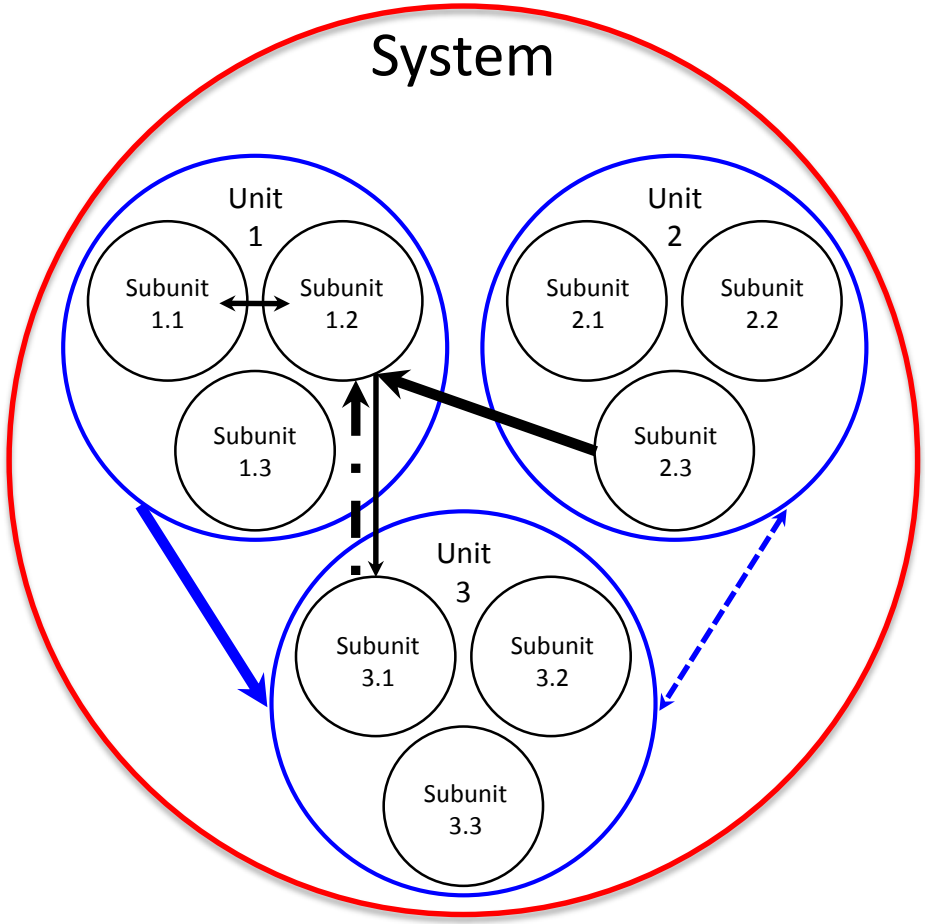
Manfred Sakel, MD, 1938, The Future of Psychiatry

SYSTEMS APPROACH TO ANXIETY

Systems Theory

- Whole > sum of parts
- Quantitative
  - Number of subsystems
  - Number of relationships
- Qualitative
  - Quality of relationships
  - Degree of integration
  - Relative efficiency in relationship to demand

Interrelatedness and Integration



Endobiogeny: Global systems theory

- Microscopic (10^{-6}-10^{-3}m)
  - Subcellular
  - Cellular
  - Tissue segments
- Mesoscopic (10^{-3}-10^{-1}m)
  - Gross tissue
  - Organs
  - Organism
- Macroscopic (>10^{0}m)
  - Social
  - Symbiotic
  - Cosmobiologic

- Central
- Peripheral
- Endocrine
- Autonomic
- Multifactorial

Endobiogeny (cont.)

- Qualitative
  - Heuristic
  - Phenomenologic
- Quantitative
  - Biomarkers
  - Modeling

Serotonin Index. This index expresses the level of autocoid and metabolic activity of peripheral serotonin. By extension, it allows for an evaluation of the level of neuro-metabolic activity of central serotonin (through inverse association with peripheral serotonin).

$= 10$ (starter index)/(insulin index × insulin resistance index)

Evoked Histamine Index. This index expresses the active circulating level of histamine.

=(eosinophils × platelets × adaptation index)/adrenal cortex index

adaptation index = eosinophils/monocytes

=(eosinophils × platelets × eosinophils)/(adrenal cortex × monocytes)

$=(\text{eosinophils}^2 \times \text{platelets})/(\text{adrenal cortex} \times \text{monocytes})$

Lapraz JC, Hedayat KM. Endobiogeny: a global approach to systems biology (part 1 of 2). *Global advances in health and medicine : improving healthcare outcomes worldwide. 2013;2(1):64-78.*

Lapraz JC, Hedayat KM, Pauly P. Endobiogeny: a global approach to systems biology (part 2 of 2). *Global advances in health and medicine : improving healthcare outcomes worldwide. 2013;2(2):32-44.*

Global Mental Health

TABLE 1 | Moving beyond scientism and skepticism in global mental health: integrative approaches to diagnosis, pathogenesis, and intervention.

	Scientism	Skepticism	Integrative
Diagnosis	Diagnostic systems rely on essentialist categories or natural kinds. Assessment systems will be ultimately be supported by data on endophenotypes	Mental illness is expressed and experienced differently in different sociocultural contexts. Symptoms vary from time to time and place to place	Mental illness is a complex reality. Nosologies are theory bound and value laden, but may improve as the relevant science and debate advance
Pathogenesis	May approach causality in terms of covering laws. May focus on a single set of associations, such as those which characterize the health care system	May emphasize the role of sociocultural values and powers in explanations. May focus on differences in conceptualization of disorders across history and geography	Emphasizes that a broad range of factors are involved in the pathogenesis of mental disorders, with causal mechanisms operating at multiple interacting levels
Intervention	May take a single bullet approach, looking for focused interventions, whether biological or community focused that will target the essence of the disorder	May emphasize that interventions reflect local values and powers. Both biological and community-focused interventions reinforce existing societal structures	Incorporates a range of insights about the nature of mental disorders, and targets a broad range of factors involved in their pathogenesis, including biological and social ones

Stein DJ, Illes J. Beyond Scientism and Skepticism: An Integrative Approach to Global Mental Health. *Frontiers in psychiatry. 2015;6:166.*

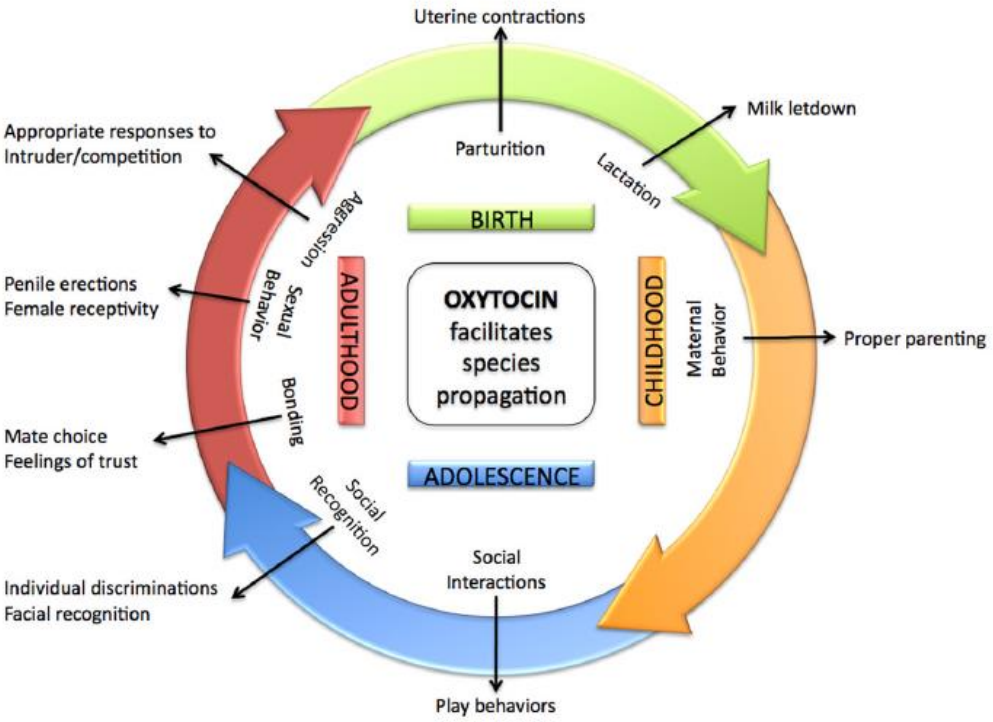
Systems Integration in Psychiatry

- 1850's: NeuroPsychoPharmacology
- 1938: BioPsychoPharmacology[19]
- 1963: Benzodiazepines
- 1969: Endocrino-Psychiatry
- 2000's: Integrated Network Psychiatry[24]

19. Sakel M. Insulin Therapy in the Future of Psychiatry. *Canadian Medical Association journal.* 1938;39(2):178-179.
24. Looijestijn J, Blom JD, Aleman A, Hoek HW, Goekoop R. An integrated network model of psychotic symptoms. *Neuroscience and biobehavioral reviews.* 2015;59:238-250.

Systems Integration (cont.)

- Brain sequestered, *not* isolated
- Neurohormones
  - Dopamine
  - TRH
  - Oxytocin
- Neurosteroids
  - Cortisol
  - Aldosterone
  - Testosterone

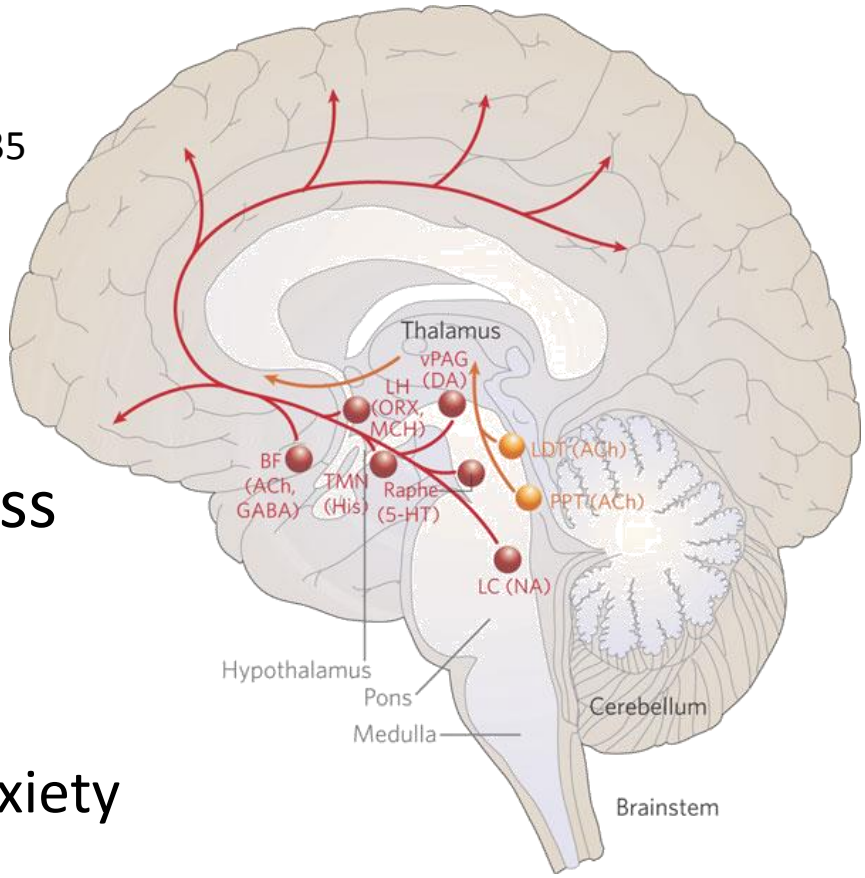


Lee HJ, Macbeth AH, Pagani JH, Young WS, 3rd. Oxytocin: the great facilitator of life. *Progress in neurobiology. 2009;88(2):127-151.*

TRH, HISTAMINES AND ANXIETY

Alpha Sympathetic: Noradrenalin

- Physiologic: ↑ SNR* [34]
  - ↑ environmental sensitivity[35]
  - ↓ feedback excitation
  - ↓ feedback inhibition[34]
  - ↑ afferent input
- Sustained sensory awareness
- Cognitive flexibility[36]
- Supraphysiologic
  - False-positive ↑ SNR* → Anxiety



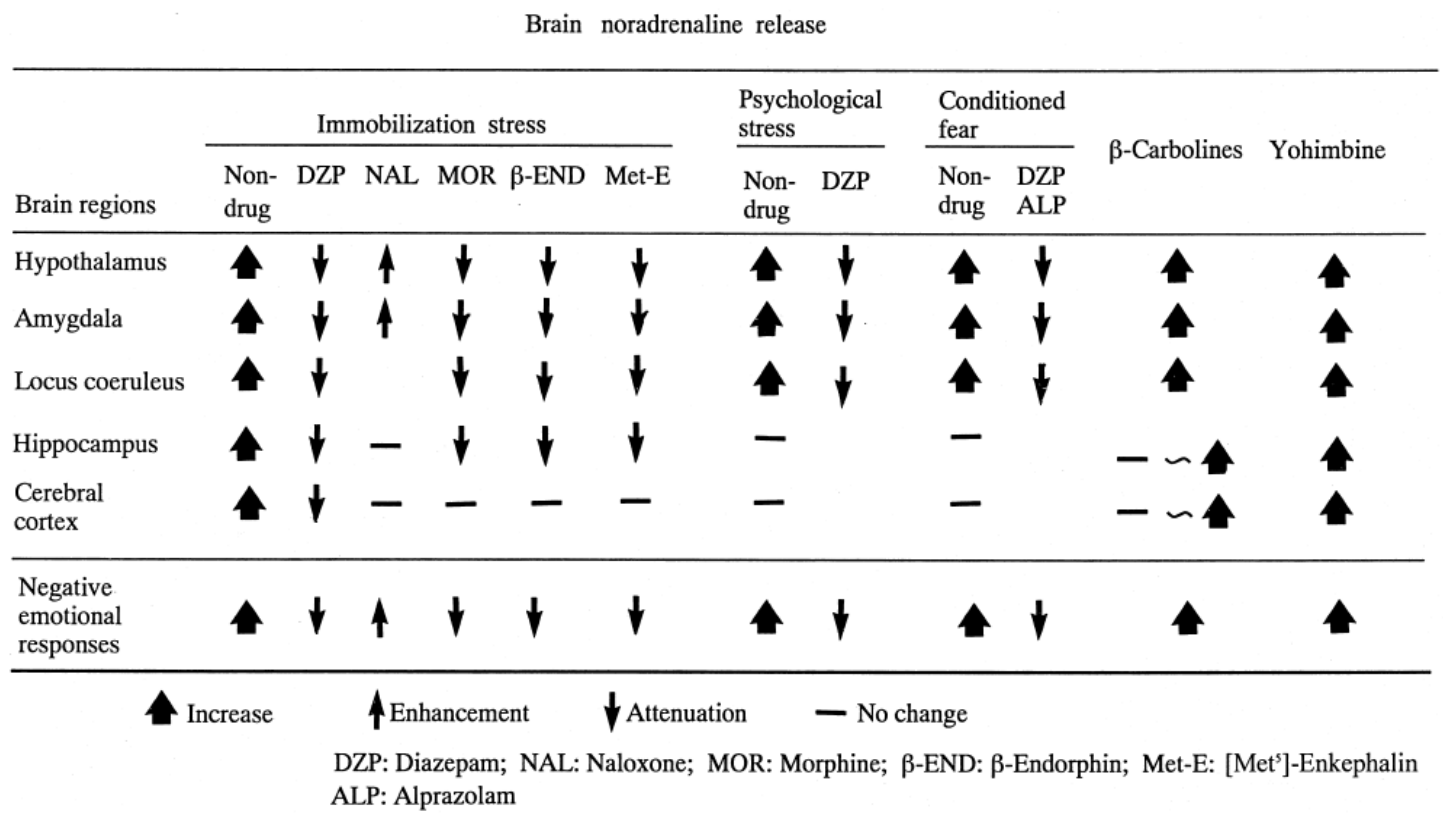
Saper et al (2005))

34. Hasselmo ME et. al. *Journal of neurophysiology.* 1997;77(6):3326-3339.
35. Aston-Jones G et. al. *Journal of neuroscience* 1981;1(8):887-900.
36. Beversdorf DQ et. al. *Neuroreport.* 2002;13(18):2505-2507.

*SNR: *Signal-to-Noise Ratio*

Anxious Behavior and NA

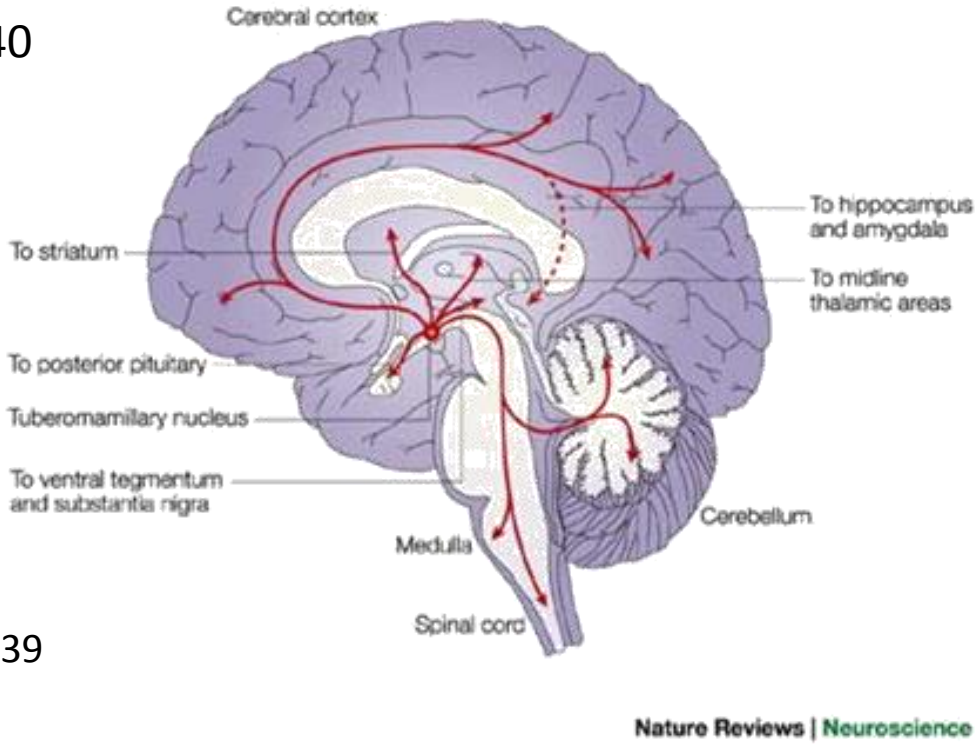
Table 1
Changes in brain noradrenaline release and behavior caused by various stresses and anxiogenic drugs and their modifications by drugs



37. Tanaka M, Yoshida M, Emoto H, Ishii H. Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. *European journal of pharmacology.* 2000;405(1-3):397-406.

Histamines and Arousal States

- Origin: Hypothalamus[40]
- Highly conserved[40]
- Wide distribution
- Role
  - Arousal, Alertness
  - Cognition, Memory
  - Mood, Pain perception[39]



39. Panula P, Nuutinen S. The histaminergic network in the brain: basic organization and role in disease. *Nature reviews. Neuroscience.* 2013;14(7):472-487.

40. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. *Physiological reviews.* 2008;88(3):1183-1241.

Histamines: Cognitive-Behavioral

- Physiologic: α-brainwave[1,2]
  - Calm alertness
  - Novelty-induced arousal
- Supraphysiologic:
  - ↓ pleasure and reward
  - ↑ anxiety and aversive behavior.[1,3]

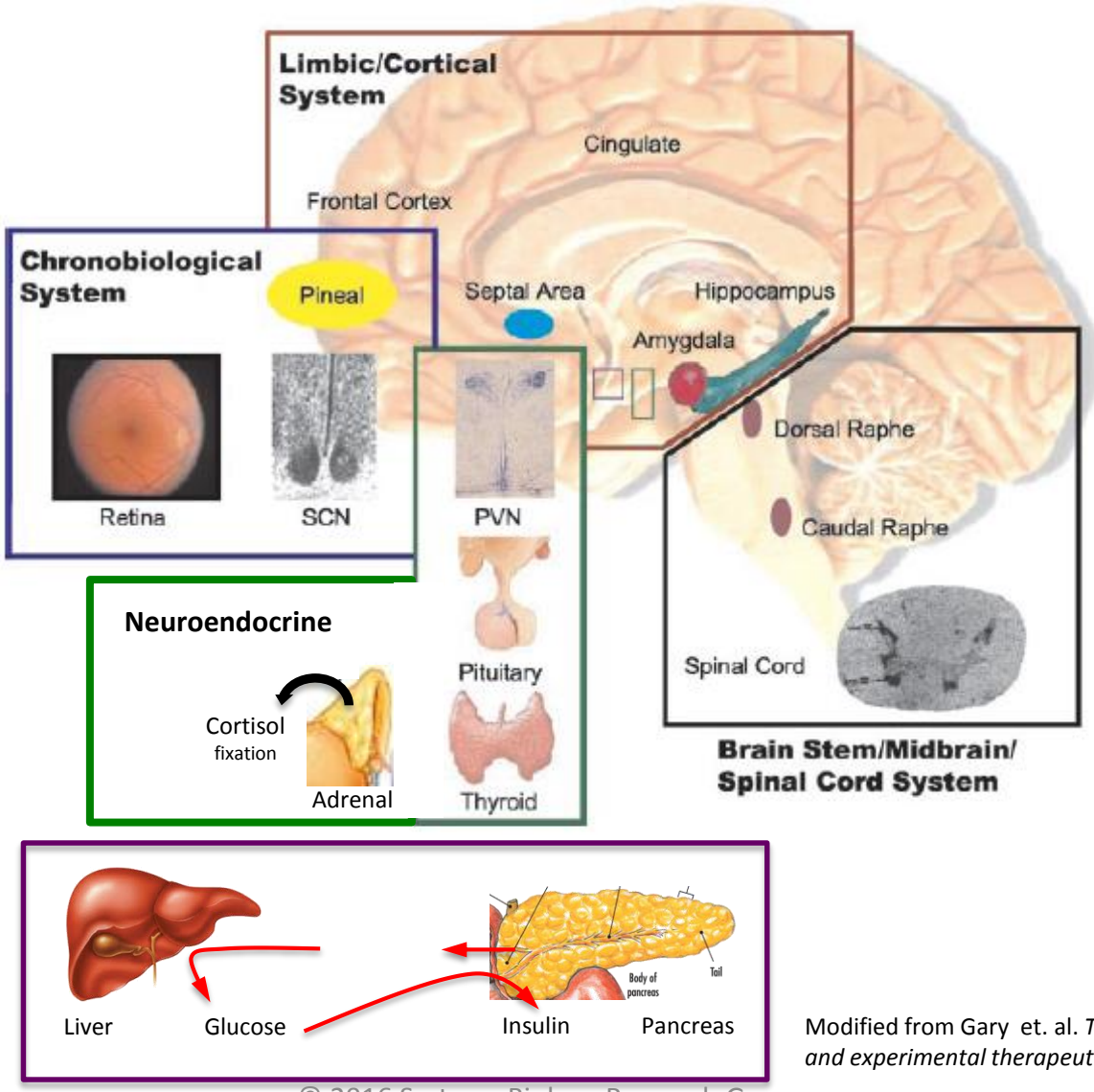
1. Haas HL et. al. Histamine in the nervous system. *Physiological reviews.* 2008;88(3):1183-1241.
2. Takahashi K et. al. Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2006;26(40):10292-10298.
3. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. *Progress in neurobiology.* 2001;63(6):637-672.

Special role of TRH

- Neuropeptide/Neurohormone (1969) [27]
- Ancient evolutionary lineage[25,26]
- Neuromodulator
- Receptors
  - Central: 65% extra-pituitary[28]
  - Peripheral[28]

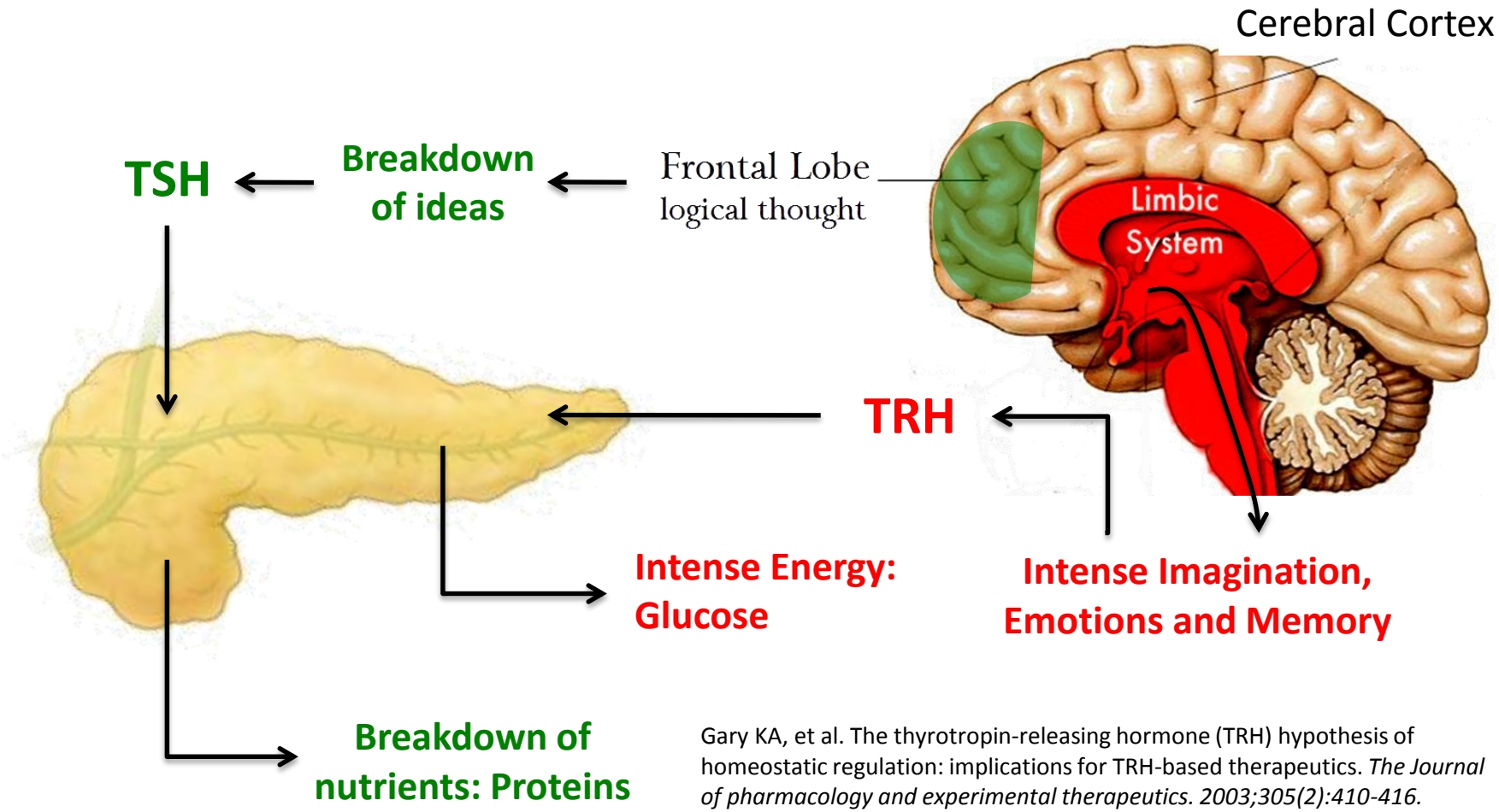
25. Lackey DB. Isolation and structural determination of a novel TRH-like tripeptide, pyroGlu-Tyr-Pro amide, from alfalfa. *The Journal of biological chemistry.* 1992;267(25):17508-17511.
26. Verburg-van Kemenade BM, Jenks BG, Visser TJ, Tonon MC, Vaudry H. Assessment of TRH as a potential MSH release stimulating factor in Xenopus laevis. *Peptides.* 1987;8(1):69-76.
27. Winokur A. Thyrotropin Releasing Hormone (TRH). 2013; 12/19/2013:inhn.org. Accessed 4 January, 2016.
28. Gary KA, Sevarino KA, Yarbrough GG, Prange AJ, Jr., Winokur A. The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. *The Journal of pharmacology and experimental therapeutics.* 2003;305(2):410-416.

Integrated Central-Peripheral TRH



Modified from Gary et. al. *The Journal of pharmacology and experimental therapeutics. 2003;305(2):410-416.*

Exocrine Pancreas-CNS 2



Gary KA, et al. The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. *The Journal of pharmacology and experimental therapeutics. 2003;305(2):410-416.*

TRH Function

- Neuromodulator
  - Mood
  - Pain
  - Quality and Rate of awareness, perception, planning, association, action
- *Accelerator of neuronal metabolic function*
- Anxiety: manage and regulate[29,30]

29. Sattin A, Senanayake SS, Pekary AE. Lithium modulates expression of TRH receptors and TRH-related peptides in rat brain. *Neuroscience.* 2002;115(1):263-273.
30. Gutierrez-Mariscal M, de Gortari P, Lopez-Rubalcava C, Martinez A, Joseph-Bravo P. Analysis of the anxiolytic-like effect of TRH and the response of amygdalar TRHergic neurons in anxiety. *Psychoneuroendocrinology.* 2008;33(2):198-213.

TRH somatic symptoms by receptor type and region of distribution

Receptor	CNS	Symptom
TRH R1	Pituitary → Peripheral hyperthyroidism	Tremors Tachycardia
	Cranial nerves	Twitching: eyelid, lip, etc.
	Vagus nerve, motor nucleus	Diarrhea Sweating
	Adrenal medulla	Tachycardia, Hyperdynamic heart Rush of blood to the head
	Pancreas, endocrine	Hyperglycemia (Glucagon) Hypoglycemia (Insulin)
TRH R2	Frontal cortex	Rapid thoughts Hyper-loquaciousness
	Hippocampus	Recall of past events
	Reticular activating system	Hyper-alertness Insomnia
	Retina	Altered Chronobiology: • Seasonal psychiatric disorders, • Insomnia
	Cerebellum	Clumsiness

31. Sun Y, et. al. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2009;34(6):1601-1608.

32. Sun Y et al. *Journal of molecular endocrinology.* 2003;30(2):87-97.

Knock Out Rats

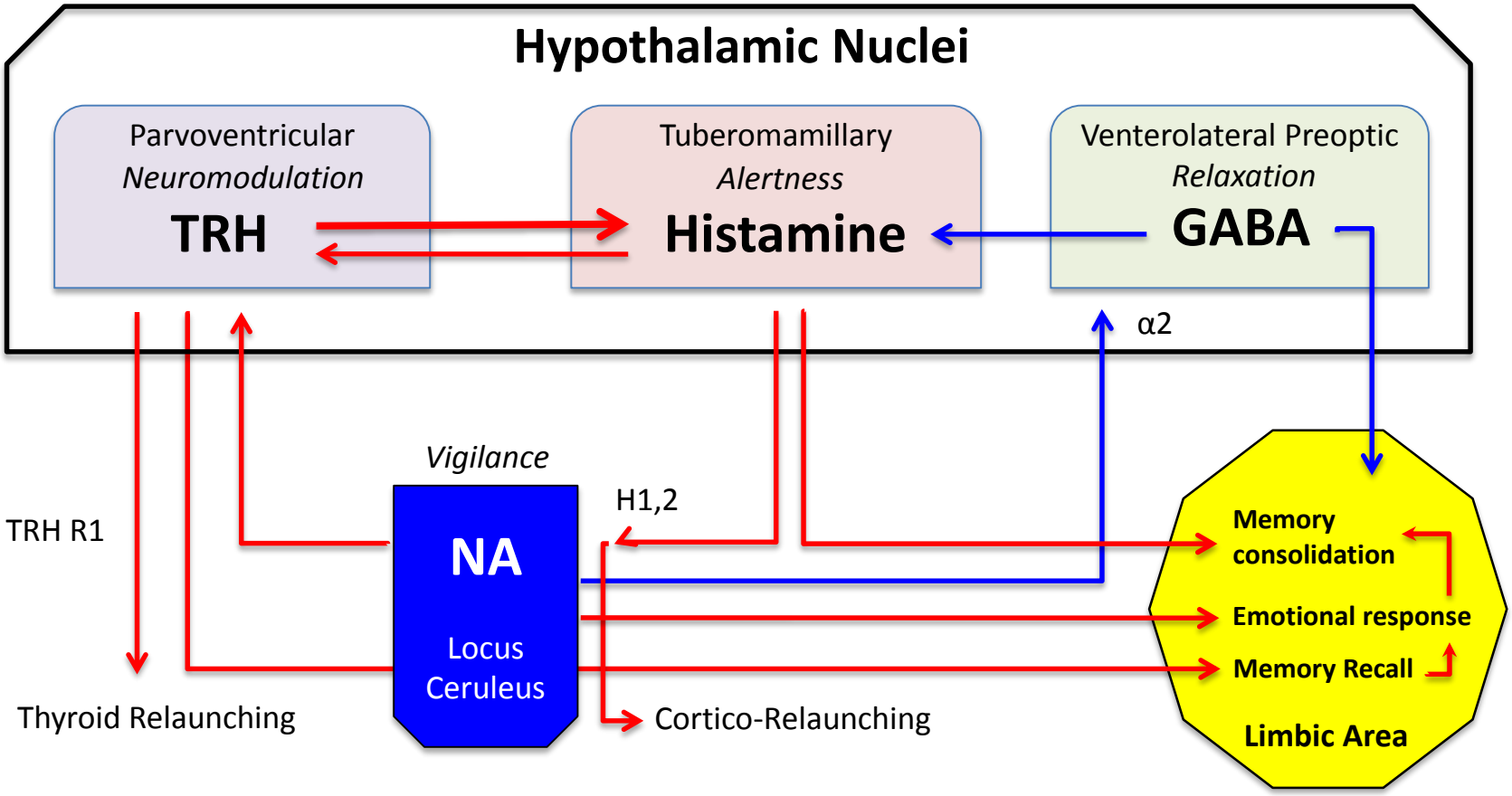
- KO* TRH R1:
  - Hypothyroid
  - Hyperglycemic
  - Anxious[33]
- Female KO* TRH R2
  - *Lower* anxiety[31]

- Conclusions
  - TRH Neurohormone (R1): not anxiogenic
  - TRH Neurotransmitter (R2): *potentially* anxiogenic

31. Sun Y, Zupan B, Raaka BM, Toth M, Gershengorn MC. TRH-receptor-type-2-deficient mice are euthyroid and exhibit increased depression and reduced anxiety phenotypes. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2009;34(6):1601-1608.
33. Zeng H, Schimpf BA, Rohde AD, Pavlova MN, Gragerov A, Bergmann JE. Thyrotropin-releasing hormone receptor 1-deficient mice display increased depression and anxiety-like behavior. *Molecular endocrinology.* 2007;21(11):2795-2804.

*KO: Knock out

TRH, NA, Histamine



KEY Stimulation → Inhibition →

***Key**: GABA: γ-Aminobutyric acid, NA: Noradrenaline, TRH: Thyrotropin Releasing Hormone*

Somatic Anxiety symptoms related to the interplay of NA, TRH and Histamine

Category	Symptom	NA	Histamine	TRH	Other
Autonomic Arousal	Palpitations	◆	*Indirect via effect on NA*	◆	
	Sweating	◆		◆	Reactive πΣ
	Trembling	◆		◆	Insufficient βΣ
	Dry mouth	◆			
Chest/ Abdomen	Dyspnea	◆			Insufficient βΣ
	Chest pain	◆			
	Nausea	◆	◆	◆	
Brain and Mind	Dizzy, Light-headed	◆			Low cortisol
	Derealization	◆	◆	◆	Insufficient Dopamine Insufficient βΣ
	Fear of loosing control, of Dying	◆	◆	◆	Excess Dopamine
General	Hot flashes	◆	◆	◆	Reactive πΣ
	Numbness, Tingling	◆	◆		Diminished circulation
	Muscle tension	◆	◆		Insufficient βΣ
	Restlessness of muscles	◆	*Indirect via effect on NA*	◆	Insufficient βΣ
	Insomnia from excessive worry	◆	◆	◆	Dopamine, Glutamate, Insufficient GABA

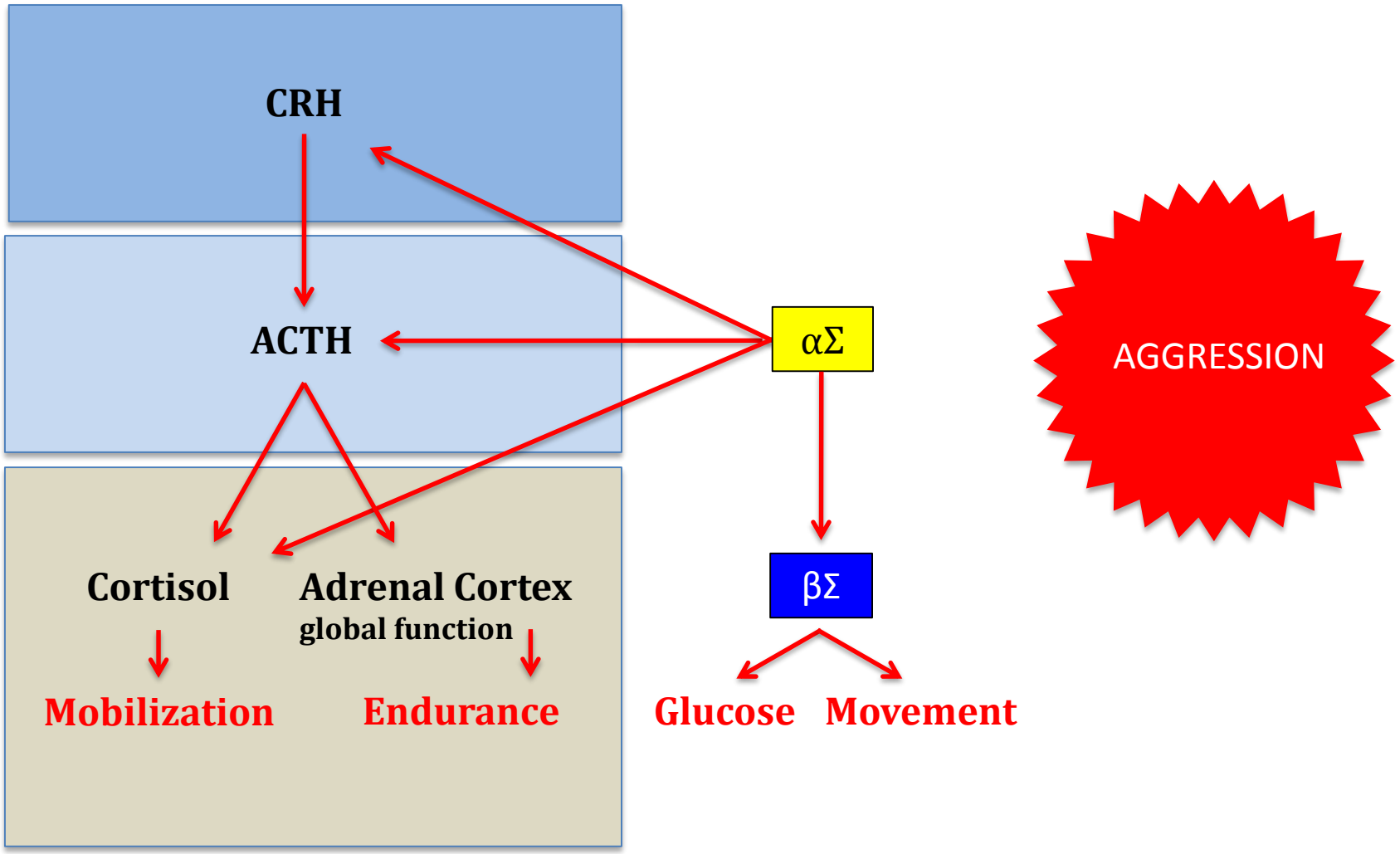
Key: βΣ: beta sympathetic, πΣ: parasympathetic, GABA: γ-amino-butyric acid, NA: Noradrenalin (αΣ), TRH: Thyrotropin releasing hormone

TRH and Depression

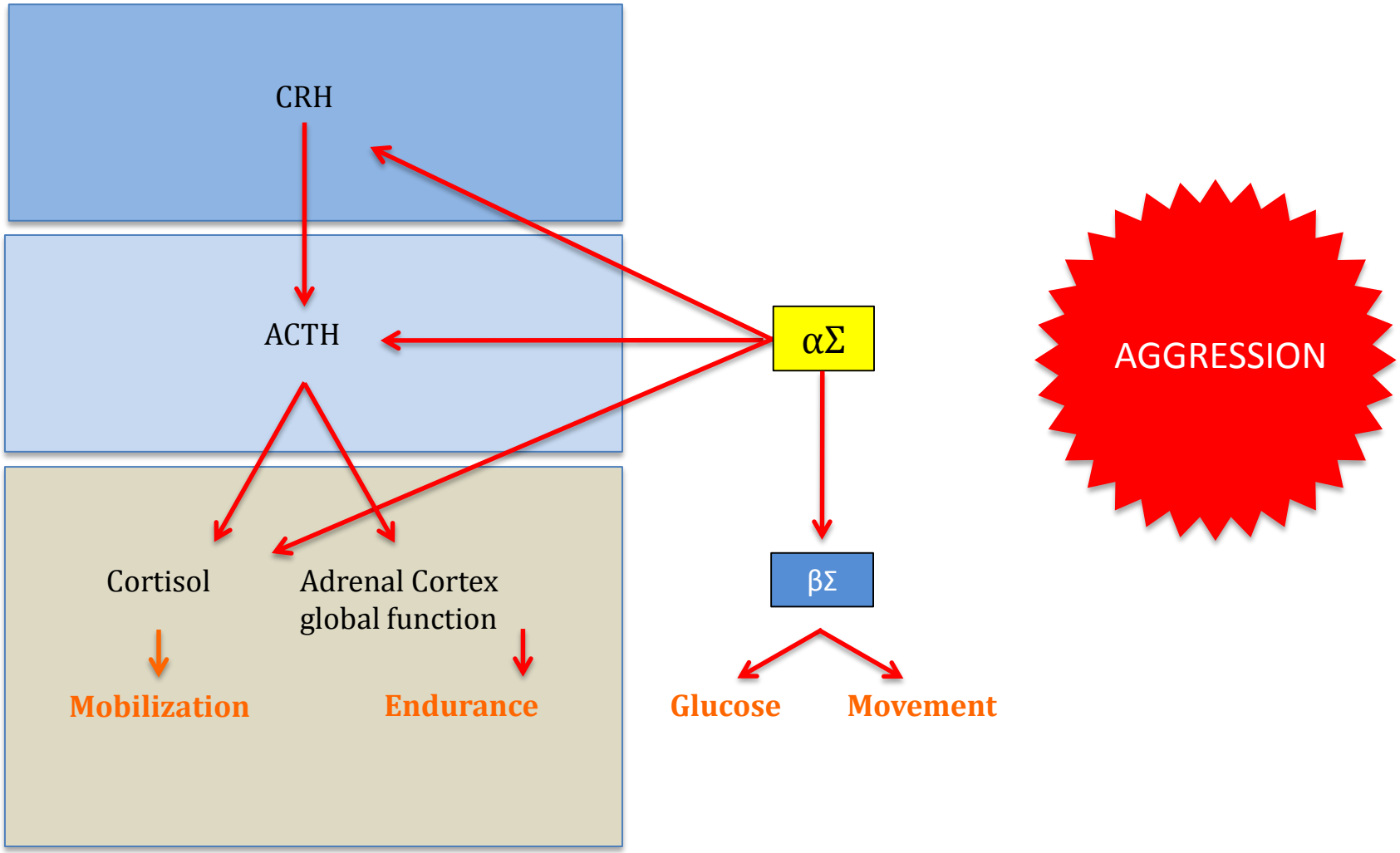
- Associated with depression[1-3]
  - TRH therapy supraphysiologic
  - *Inhibits* TRH
- Endobiogeny:
  - TRH-Serotonin[4]
  - TRH-Pancreas[2]

1. Marangell LB et al. Effects of intrathecal thyrotropin-releasing hormone (protirelin) in refractory depressed patients. Archives of general psychiatry 1997;**54**(3):214-22.
2. Daimon CM et al. The role of Thyrotropin Releasing Hormone in aging and neurodegenerative diseases. American journal of Alzheimer's disease 2013;**1**(1).
3. Duval F et al. Cortisol hypersecretion in unipolar major depression with melancholic and psychotic features: dopaminergic, noradrenergic and thyroid correlates. Psychoneuroendocrinology 2006;**31**(7):876-88.
4. Sattin A, Pekary AE, Blood J. Escitalopram regulates expression of TRH and TRH-like peptides in rat brain and peripheral tissues. *Neuroendocrinology. 2008;88(2):135-146.*

REVIEW: Adaptive response to aggression

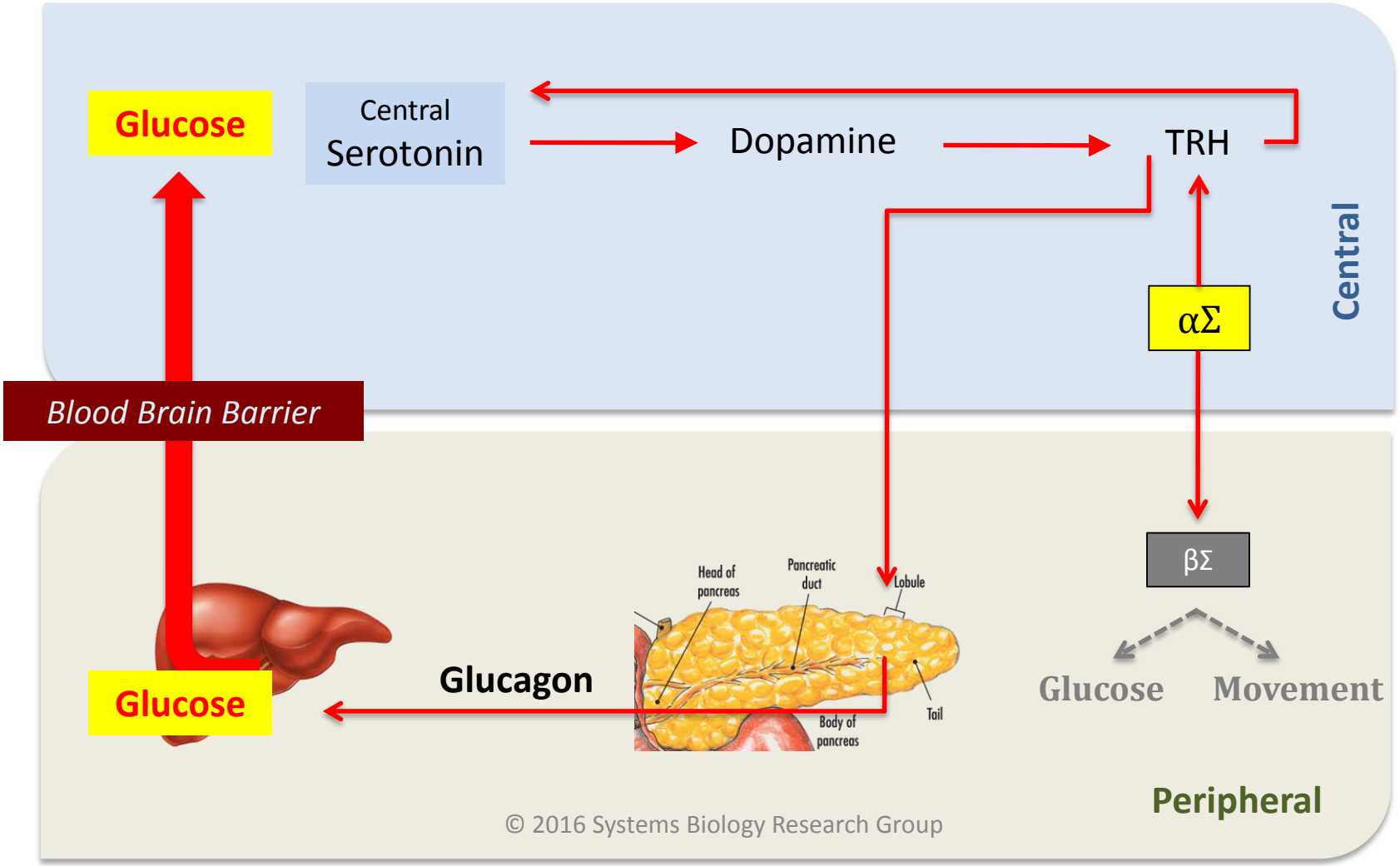


Central depression: Type 1 DISADAPTATION



Hori H, et al. *Journal of affective disorders. 2014;152-154:441-447.*

Central Depression: Reduction of Central Serotonin



CLINICAL PRACTICE

Top 6 symptoms: Thyrotropic and Pancreas

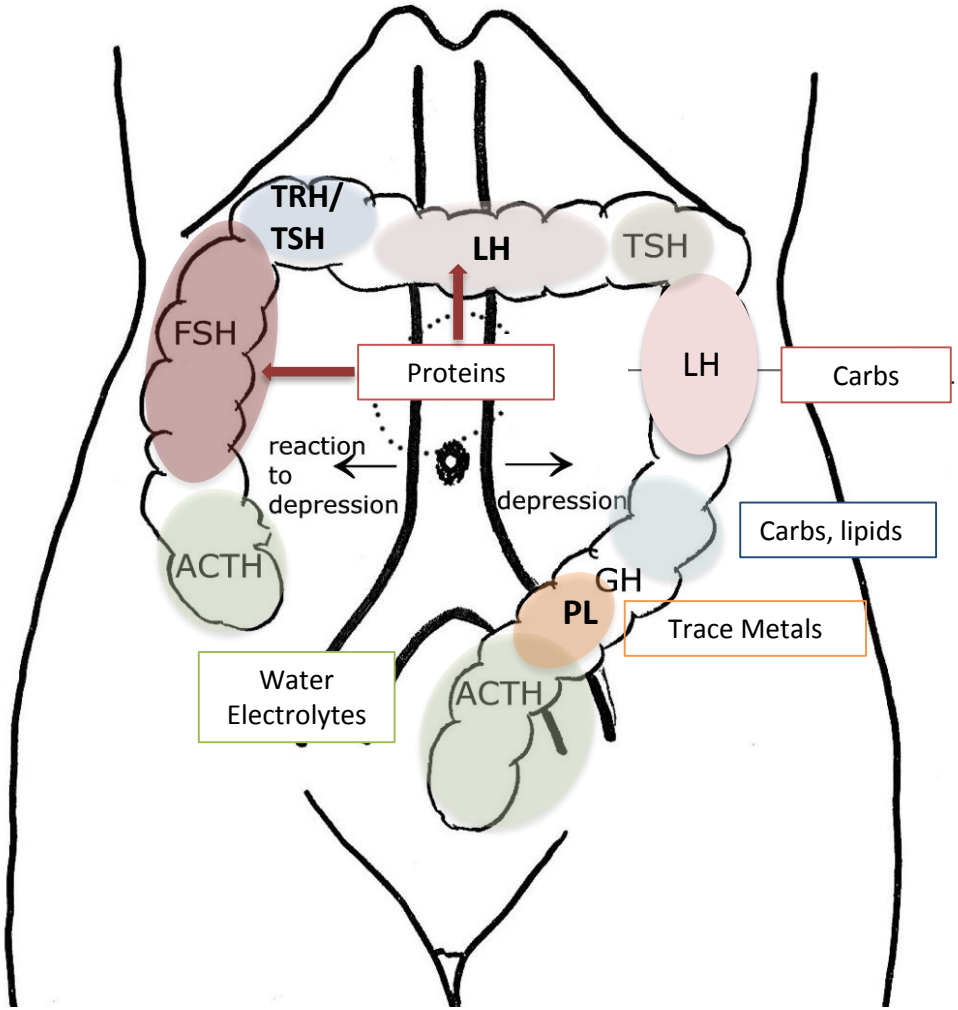
Symptom	TRH	TSH	T4	T3	Pancreas
Dreams: in color, vivid and/or with sound	↑				
Anxiety with tremors	↑			±	
Explosive anger	↑				◆
Mucous with dairy		↑			◆
Heat intolerance			↑		
Cold intolerance				↑	

Top 6 signs:
Thyrotropic and Pancreas

Symptoms	TRH	TSH	T4	T3	Pancreas
Colon, hepatic flexure	↑				
Deep tendon reflex, brisk	↑			±	
Tenderness, pesorinum		↑	↑		
Tenderness to right of umbilicus					Exocrine
Tenderness to left of umbilicus					Endocrine

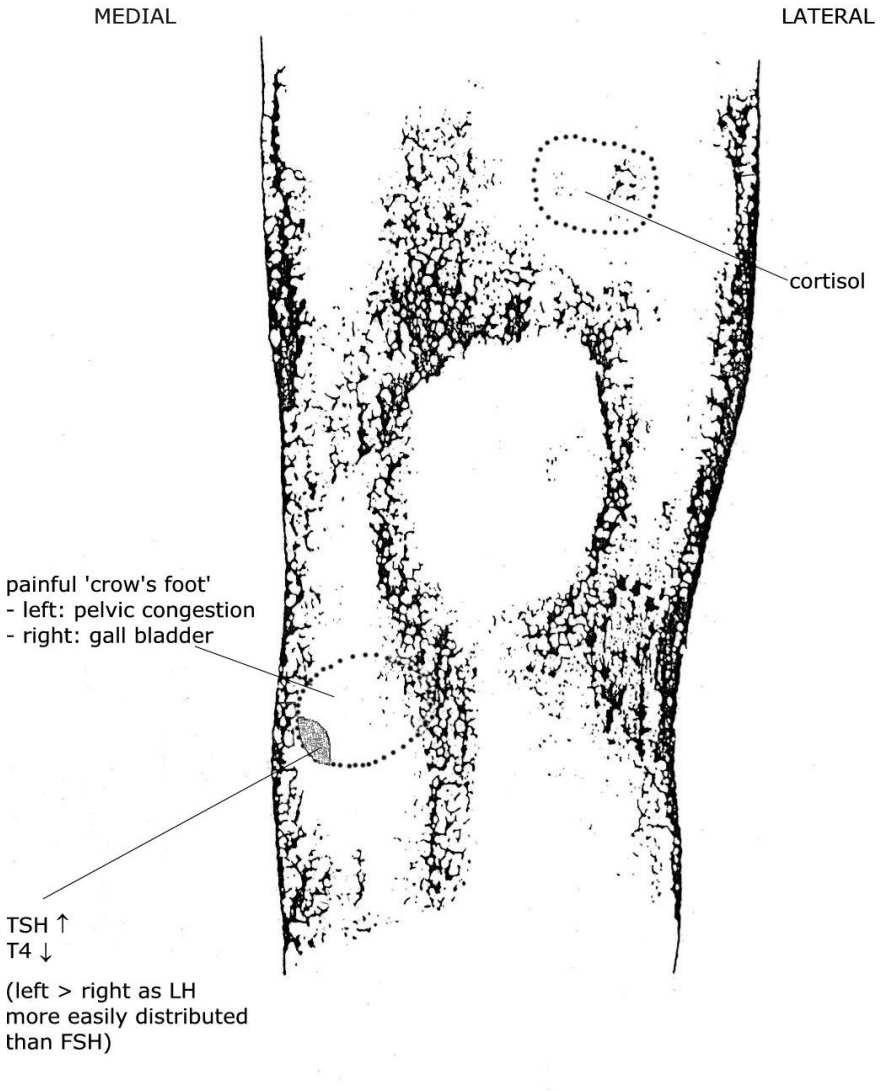
Expert opinion only

Cartography of Endo-Enteric relationships



Expert opinion only

Peripheral Signs

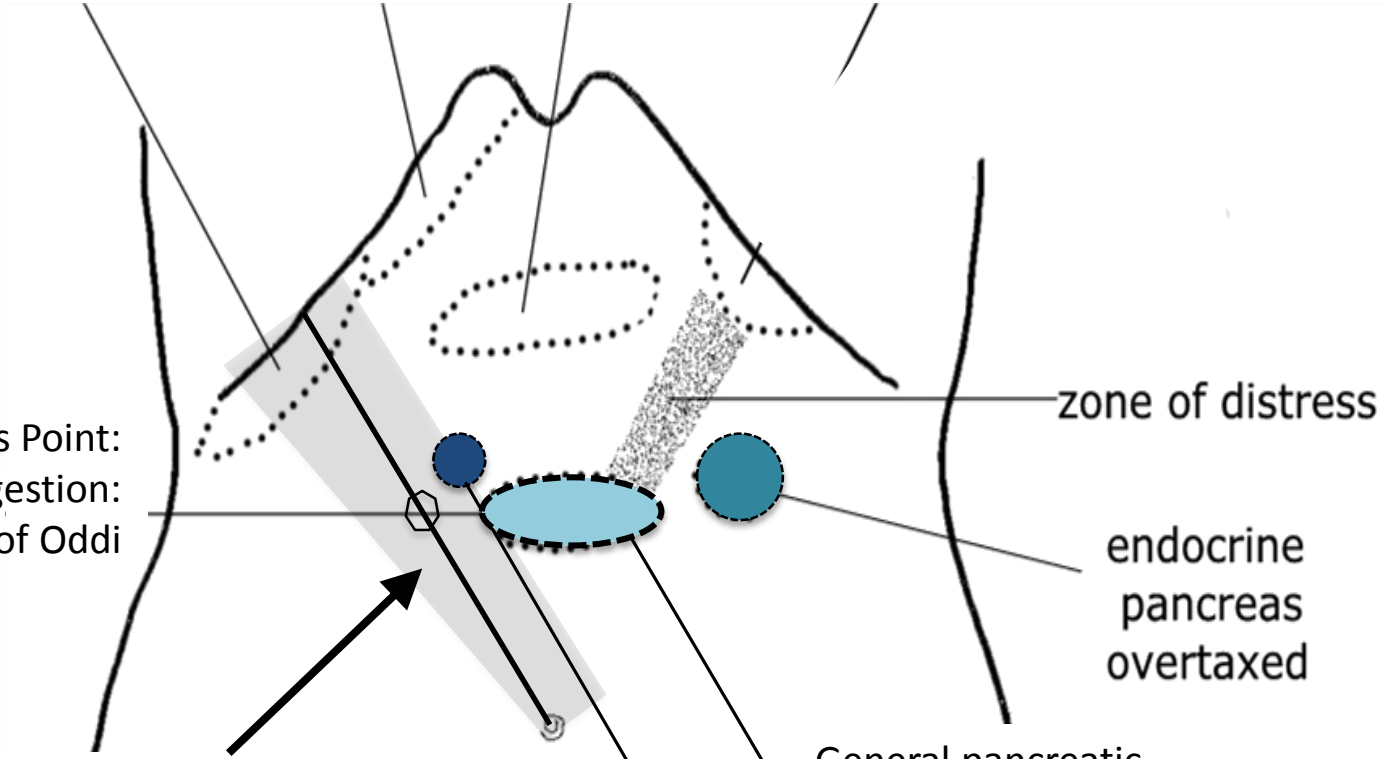


Liver congestion:
Secretory

Liver congestion:
Circulatory

Splanchnic congestion →
hepato-pancreatic blockage

Expert opinion only:
based on superficial referral points of viscera



Murphy's Point:
Congestion:
Sphincter of Oddi

Hepatic congestion, extra-hepatic:
Sphincter of Oddi, Splanchnic congestion, Duodenal plexus

General pancreatic congestion

Exocrine pancreatic congestion

Therapeutics for TRH

- Motherwort (*Leonurus cardiaca*)
  - Reduces TRH,[1] Expressions of anxiety[1,2]
  - Tea, Tincture, Dry extract

1. Wojtyniak K, Szymanski M, Matlawska I. Leonurus cardiaca L. (motherwort): a review of its phytochemistry and pharmacology. *Phytotherapy research : PTR. 2013;27(8):1115-1120.*
2. Ovanesov KB, Ovanesova IM, Arushanian EB. [Effects of melatonin and motherwort tincture on the emotional state and visual functions in anxious subjects]. *Eksp Klin Farmakol.* 2006;69(6):17-19.

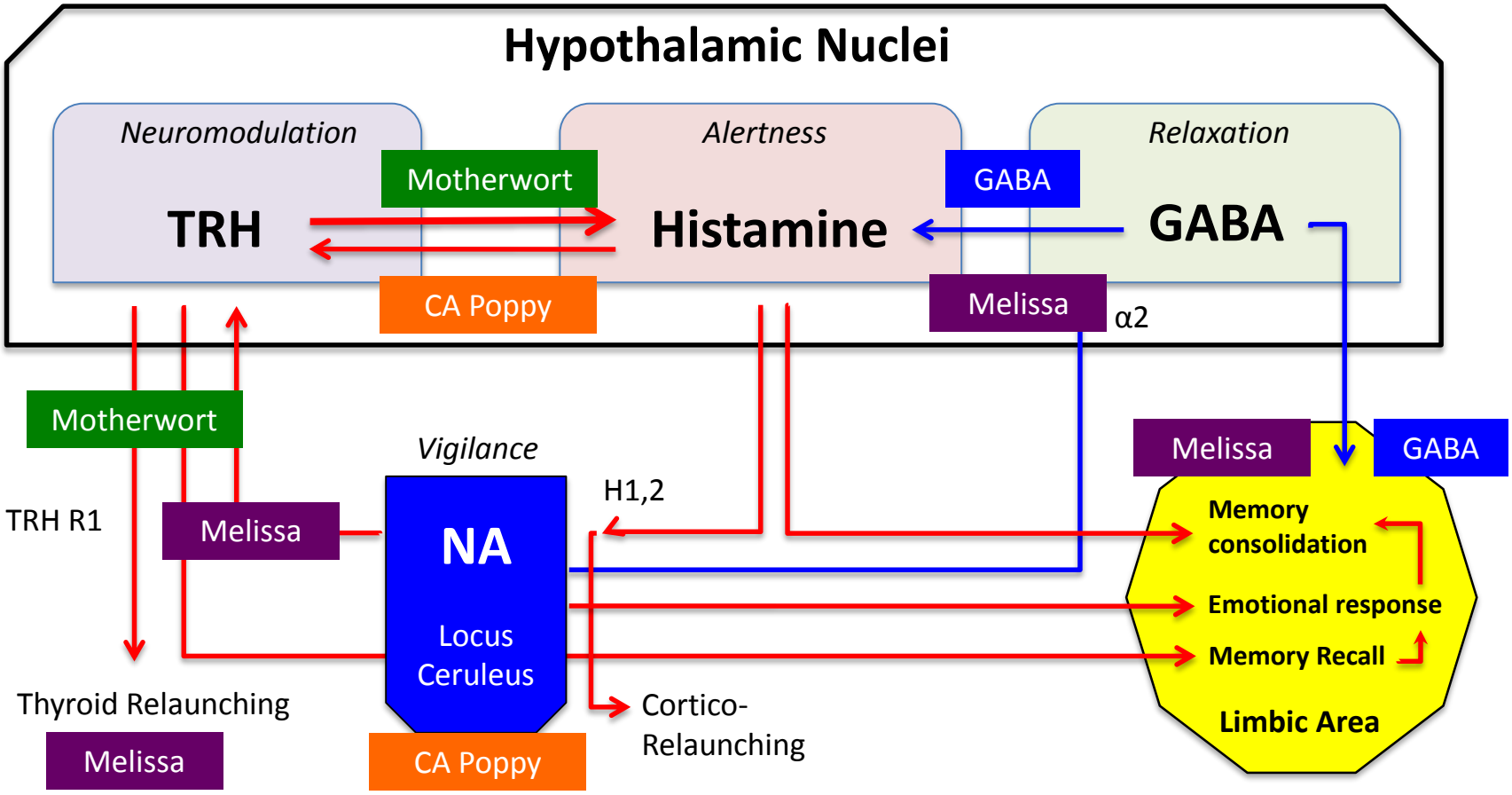
Therapeutics for TRH

- *Expert opinion only*
  - Pichi (*Fabiana imbricata*):
    - Tea, Tincture
  - Lithy tree (*Vibernum lantanum*)
    - Gemmotherapy
  - Lac caninum
    - Homeopathic: 3x-9c

Synergistic therapies

Medicinal plant	↓NA	GABA	Endorphins	Thyroid, peripheral	Pancreas
Passionflower	◆	◆			
Motherwort	◆				
California poppy	◆		◆		
Lemon balm	◆	◆		◆	
Agrimony					◆
GABA 50-100 mg BID-TID		◆			◆

Recall: TRH, NA, Histamine

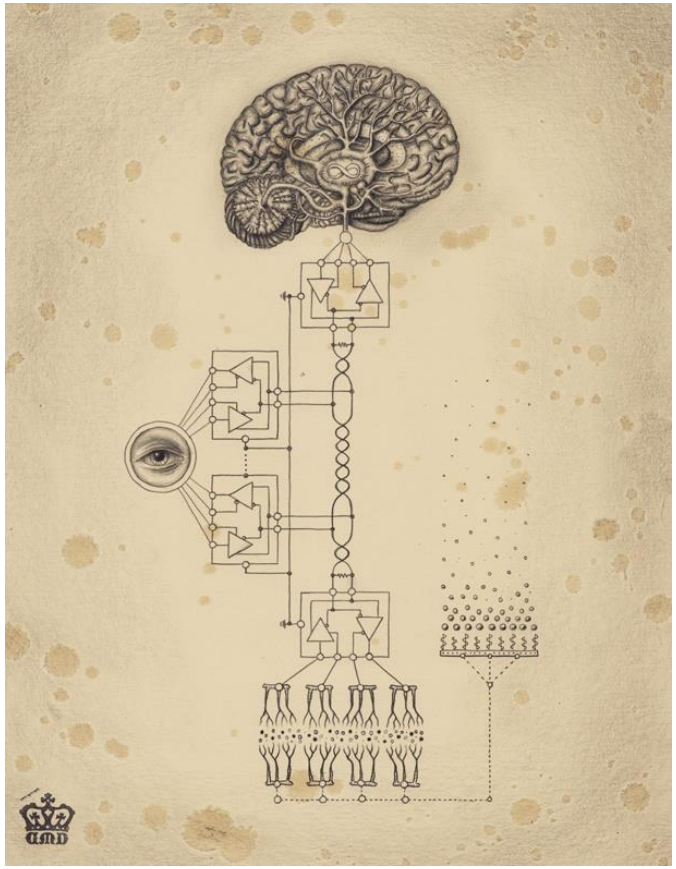


***Key**: GABA: γ-Aminobutyric acid, NA: Noradrenaline, TRH: Thyrotropin Releasing Hormone*

ENDOBIOGENIC APPROACH TO TREATMENT

General considerations in treating anxiety and depression

- Understand patient
- Do not minimize symptoms
- Respect complexity
- Evaluate origins



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Treatment priorities

- Symptomatic
  - GABA 50-100 mg BID-TID
  - Phytocalm 2 caps BID-TID
- Terrain: Anxiety
  - Alpha: Passionflower
    - Tisane: 1 tsp/1 c. water 5-8 minutes; 1 c. TID
    - Mother Tincture: 1-3 ml BID-TID in warm water
  - TRH:
    - Phytocalm 1 capsule TID
    - Lithy tree GM (Expert opinion)
      - D1: 1-3 ml BID-TID
      - Concentrate: 5-15 drops BID-TID
    - Lac caninum 9c 2 pellets BID (Expert opinion)

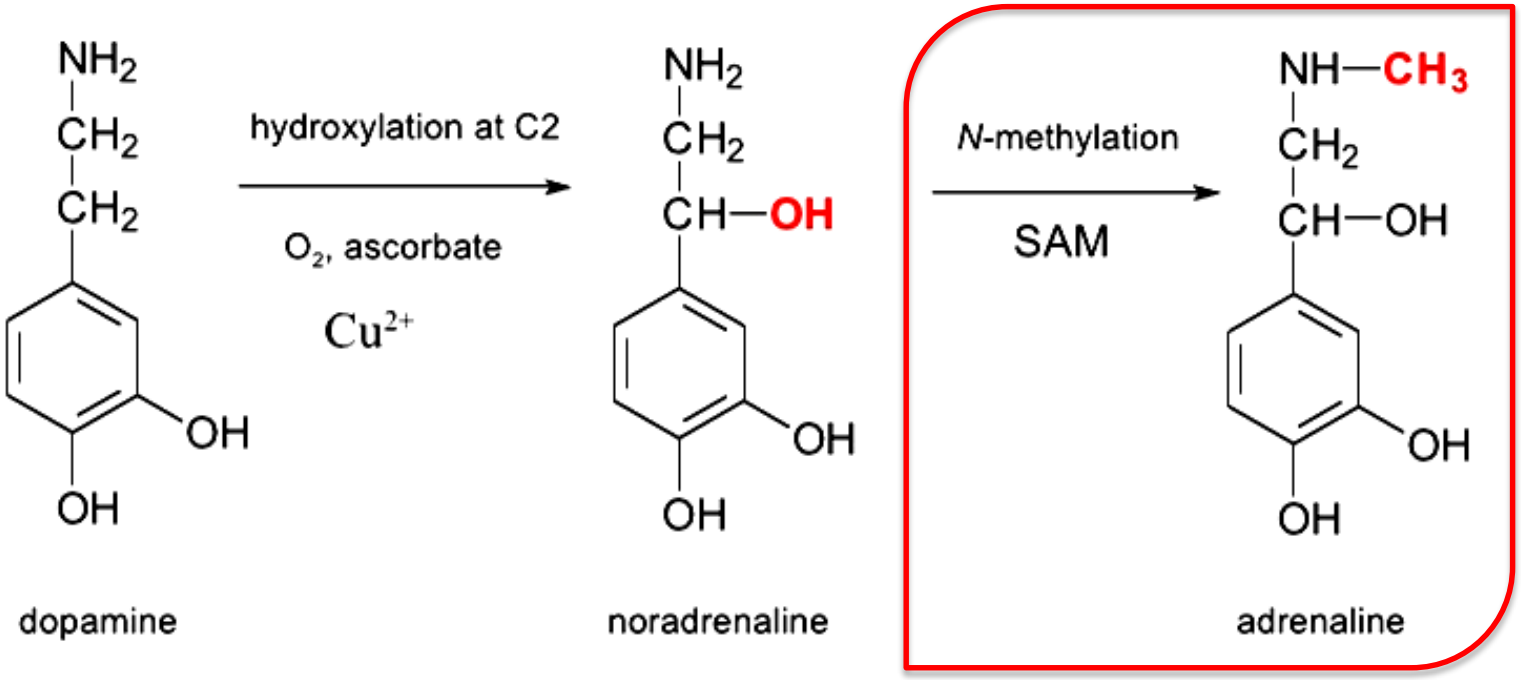
Treatment: Depression

- Beta-Sympathetic:
  - SAMe[1] 100 mg BID
- Adaptability, Adrenal cortex
  - Rhodiola rosea[2] 200 mg (4:1) 1 BID

1. AHRQ Reviews: http://archive.ahrq.gov/clinic/epcsums/samesum.pdf
2. Mao, J et al *Phytomedicine* 2015 22 (3): 394-399

Adrenaline: increased production

1. SAMe (S-adenosyl methionine)
   - Dose: 100-200 mg twice per day *before meal*



Treatment priorities

- Dietary changes
  - Small frequent meals
  - Low glycemic foods
    - Whole grains
    - Leafy green vegetables
- Psychotherapy + Skills

“The human being is entirely conditioned by his instrument of expression and can express no more than his nervous system, brain and glands permit.” Alice A. Bailey

CASE STUDY IN PHYSIOPSYCHIATRY: BIOPHENOMENOLOGY ACCORDING TO ENDOBIOGENY

Global Systems Approach to Anxiety

SCALE

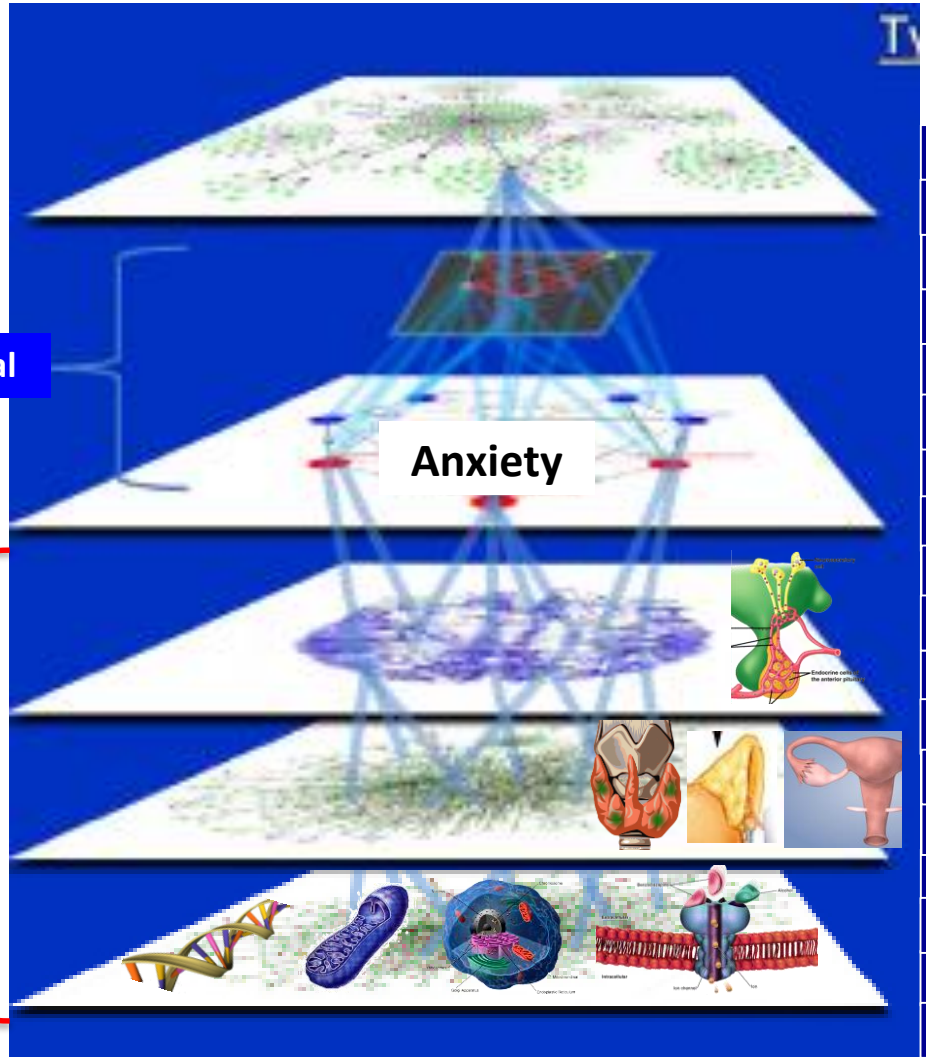
>10^0m: Macroscopic
•Cosmobiologic
•Symbiotic
•Social

Phenomenological

10^{-3}-10^{-1}m: Mesoscopic
•Organism
•Organs
•Tissues

Biological

10^{-6}-10^{-3}m: Microscopic
•Cellular
•Subcellular
•DNA



INDEX

Permeability index corr.
Entanglement score
Worry score
Cognitive diss. Index adj.
Traumatic Memory index
Thought index
Locus ceruleus index adj.
Serotonin index
Prolactin index (Dopamine)
Locus ceruleus index
Histamine Index
TRH/TSH, βMSH/αMSH
Thyroid metabolic index
Adrenal Yield
Genital ratio
Insulin / Insulin Resistance
Harmful free radical index
Passive cellular permeability

Modified from Looijestijn et. al. *Neuroscience and biobehavioral reviews. 2015;59:238-250.*

Case Study

- 32 yo female, transgender, h/o
  - Chronic Pain (10 yr)
  - Chronic fatigue Syndrome (10 yr)
  - Major depression (12 yr)
  - Generalized Anxiety Disorder (>15 yr)

- Pregabalin 100 mg qHS
- Buproprion 150 mg BID
- PRN: *prescribed by other physicians*
  - Diazepam 5 mg
  - Lorazepam 0.5 mg
  - Tramadol 50 mg
  - Cyclobenzaprine 5 mg
  - Medical marijuana

Endobiogenic Biologic Assessment

Index	10/2014	Low	High
βMSH/αMSH index	10.6	6	8
Peripheral Serotonin index	22.3	1.5	7.5
Prolactin index	0.30	0.8	1.2
Thyroid metabolic index	10.6	3.5	5.5
Adrenal yield score	41	3.15	13.50
Insulin resistance index	0.21	0.75	1.25
Harmful free radicals	288	2	6
Passive membrane permeability	110	4	9

Endobiogenic Phenomenological Assessment

Index	10/2014	Low	High
Locus ceruleus adjusted	2,970	7	450
Traumatic memory index	613	0.08	6
Permeability index adj.	506,996	1.76	1,091
Entanglement score	11,237	1,442	8,825
Cognitive dissonance adj.	1,486	10	300

Case Study (cont.) Intervention:

- *Passiflora incarnata* (Passionflower) MT
  - Anxiolytic, acts on $GABA_A$ receptors, Enhances Benzo activity[1]
  - Equivalent to Oxazepam 30 mg[2]

1. Gazolaa A, Costa G, Castellans L, et al. Involvement of GABAergic pathway in the sedative activity of apigenin, the main flavonoid from Passiflora quadrangularis pericarp. *Journal of ethnopharmacology. 2015;25(2):158-163.*
2. Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *Journal of clinical pharmacy and therapeutics. 2001;26(5):363-367.*

Case Study (cont.) Intervention:

- Phytocalm (Time Labs, Pocatello, ID)
  - Leonurus cardiaca (Motherwort)
    - Reduces TRH,[1] Expressions of anxiety[1,2]
  - *Eschscholtzia californica* (California poppy)
    - Inhibit Dopamine, Adrenaline[3]
    - Augments enkephalins (opioid-like)[4]
  - *Melissa officinalis* (Lemon balm)
    - Reduces Noradrenaline
    - Anxiolytic, GABA-ergic, Cognitive Enhancer[5,6]

1. Wojtyniak K, Szymanski M, Matlawska I. Leonurus cardiaca L. (motherwort): a review of its phytochemistry and pharmacology. *Phytotherapy research : PTR. 2013;27(8):1115-1120.*
2. Ovanesov KB, Ovanesova IM, Arushanian EB. [Effects of melatonin and motherwort tincture on the emotional state and visual functions in anxious subjects]. *Eksp Klin Farmakol.* 2006;69(6):17-19.
3. Kleber E, Schneider W, Schafer HL, Elstner EF. Modulation of key reactions of the catecholamine metabolism by extracts from Eschscholtzia californica and Corydalis cava. *Arzneimittel-Forschung. 1995;45(2):127-131.*
4. Reimeier C, Schneider I, Schneider W, Schafer HL, Elstner EF. Effects of ethanolic extracts from Eschscholtzia californica and Corydalis cava on dimerization and oxidation of enkephalins. *Arzneimittel-Forschung. 1995;45(2):132-136.*
5. Yoo DY, Choi JH, Kim W, et al. Effects of Melissa officinalis L. (lemon balm) extract on neurogenesis associated with serum corticosterone and GABA in the mouse dentate gyrus. *Neurochemical research.* 2011;36(2):250-257.
6. Awad R, Muhammad A, Durst T, Trudeau VL, Arnason JT. Bioassay-guided fractionation of lemon balm (Melissa officinalis L.) using an in vitro measure of GABA transaminase activity. *Phytotherapy research : PTR.* 2009;23(8):1075-1081.

Outcomes

- 2/2015: 4 months
  - Discontinued all PRN medications
  - Reduced anxiety, spontaneous crying, depression, pain
  - Increase mobility

Endobiogenic Biologic Assessment

Index	10/2014	2/2015	Low	High
βMSH/αMSH index	10.6	3.3	6	8
Peripheral Serotonin index	22.3	8	1.5	7.5
Prolactin index	0.30	2.47	0.8	1.2
Thyroid metabolic index	10.6	2.97	3.5	5.5
Adrenal yield score	41	12.5	3.15	13.50
Insulin resistance index	0.21	0.55	0.75	1.25
Harmful free radicals	288	4.14	2	6
Passive membrane permeability	110	14	4	9

Endobiogenic Phenomenological Assessment

Index	10/2014	2/2015	Low	High
Locus ceruleus adjusted	2,970	796	7	450
Traumatic memory index	613	18	0.08	6
Permeability index adj.	506,996	12	1.76	1,091
Entanglement score	11,237	417	1,442	8,825
Cognitive dissonance adj.	1,486	678	10	300

Follow Up

- 7 months post-treatment
  - 5/2015: D/C Buproprion (self-managed)
- 9 months post-treatment, 2 months off Buproprion
  - 7/2015: Worsening of symptoms

Endobiogenic Biologic Assessment

Index	10/2014	2/2015	7/2015	Low	High
βMSH/αMSH index	10.6	3.3	3.0	6	8
Peripheral Serotonin index	22.3	8	41.2	1.5	7.5
Prolactin index	0.30	2.47	0.22	0.8	1.2
Thyroid metabolic index	10.6	2.97	2.92	3.5	5.5
Adrenal yield score	41	12.5	45	3.15	13.50
Insulin resistance index	0.21	0.55	0.03	0.75	1.25
Harmful free radicals	288	4.14	139	2	6
Passive membrane permeability	110	14	201	4	9

Endobiogenic Phenomenological Assessment

Index	10/2014	2/2015	7/2015	Low	High
Locus ceruleus adjusted	2,970	796	22,313	7	450
Traumatic memory index	613	18	1,671	0.08	6
Permeability index adj.	506,996	12	26,768,145	1.76	1,091
Entanglement score	11,237	417	52	1,442	8,825
Cognitive dissonance adj.	1,486	678	6,350	10	300

Sourcing Products

Therapeutic	Sources
Tisanes	Starwest Botanicals: www.starwest-botanicals.com Mountain Rose: www.mountainroseherbs.com
Tincture	Time Labs: www.timelabs.com Seroyal: www.seroyal.com Wise woman: www.wisewomanherbals.com
Phytocalm	Time labs: www.timelabs.com
Gemmotherapy	Time labs: www.timelabs.com Seroyal: www.seroyal.com Herbal Gems (concentrates): http://gemmos-usa.com/category/products/herbalgem/

CONCLUSION

Conclusions

- Anxiety multifactorial
  - Biological
  - Phenomenological
- Future of Integrative Psychiatry
- Global systems theory
- Research into Endobiogeny

Discussion, Thoughts and Questions

- Learn More
  - www.endobiogeny.com
  - www.learnendo.lt
- Global Training Initiative
  - kmhedayat@fshcenter.com
  - info@endobiogeny.com