Neurological Health and Pathophysiology

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Financial Disclosure

• Consultant for Restorative Formulations

• I have been a Natural Products and Cannabis Industry Consultant, for GMPs, Regulatory Issues, Pharmacology, Research Initiatives, New Product Development and Formulation

• I have financial interests in the Natural Products Industry
Introduction

Other Targets

Depression

Anxiety

Endocannabinoid System

Care & Feeding of the CNS

Mind Map of Lecture
# Health as a Continuum

## Health

| +++++ | Perception | ++ | + | - | - | - | Perception | - - - |
| +++++ | Background Mood | ++ | + | - | - | - | Background Mood | - - - |

### Allostasis/Resilience
- Energetic Disturbance
- Functional Disturbance
- Biochemical Disturbance
- Histological Disease

## The Wall

## Disease

### Optimal Wellness
- Detoxification Phase
- Acute Defensive Reaction Phase

### Subclinical
- Compensation Phase
- Decompensation Phase
- Degeneration Phase

### Clinical
- Autoimmune Neoplastic Phase

Informational flow dynamics:
- Catecholamines, corticoids, NTs, peptides
- Gut, endocrine, immune

Informational flow disruption

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Comorbidity and shared pathways to illness

Depression is highly comorbid with:

- heart disease
- type 2 diabetes
- obesity
- metabolic syndrome
Special Articles

Initiation and Adaptation: A Paradigm for Understanding Psychotropic Drug Action

Steven E. Hyman, M.D., and Eric J. Nestler, M.D., Ph.D.

Objective: This article describes a paradigm—initiation and adaptation—within which to conceptualize the drug-induced neural plasticity that underlies the long-term actions of psychotropic drugs in the brain. Method: Recent advances in neurobiology are reviewed. Results: Recent developments in cellular and molecular neurobiology provide new conceptual and experimental tools for understanding the mechanisms by which psychotropic drugs produce long-lived alterations in brain function. Because of the availability of more robust animal models, the mechanisms by which drugs of abuse produce dependence are better understood than the mechanisms by which antidepressants, antipsychotics, and lithium produce their therapeutic effects. Nonetheless, the fundamental types of mechanisms appear to be similar: chronic drug administration drives the production of adaptations in postreceptor signaling pathways, including regulation of neural gene expression. Whether the results are deleterious
A Paradigm for Understanding Psychotropic Drugs

Stephen Hyman, former director of the NIMH, 1996:

- Psychiatric medications “create perturbations in neurotransmitter functions.”

- In response, the brain goes through a series of compensatory adaptations in order “to maintain their equilibrium in the face of alterations in the environment or changes in the internal milieu.”

- The “chronic administration” of the drugs then cause “substantial and long-lasting alterations in neural function.”

- After a few weeks, the person’s brain is now functioning in a manner that is “qualitatively as well as quantitatively different from the normal state.”

1949 - A Nobel Prize in Medicine was given to Egas Moniz for inventing the frontal lobotomy

Today - A 20 y/o who goes on disability for mental illness will collect over $1,000,000 in 40 yr
The Disabled Mentally Ill in the Prozac Era
SSI and SSDI Recipients Under Age 65 Disabled by Mental Illness, 1987–2007
Is the Model Working

Children on SSI that were disabled due to mental illness

- 1987: 5.5% of total on SSI
- 2007: 50% of total on SSI

Social Security Administration reports 1987 - 2007
Leading cause of global disability

A YLDs

- Depressive disorders
- Anxiety disorders
- Schizophrenia
- Bipolar disorder
- Eating disorders
- Childhood behavioural disorders
- Pervasive developmental disorders
- Idiopathic intellectual disability
- Alcohol use disorders
- Drug use disorders
- Other mental disorders

Percentages and ranges are provided for each category.
It is both compelling and daunting to consider that dietary intervention at an individual or population level could reduce rates of psychiatric disorders.”

AJP 2010
Etiology Includes Food In:

- CVD
- Stroke
- Obesity
- Type 2 Diabetes
- Metabolic Syndrome
- Some cancers

Dementia/Depression/Anxiety
+ ≠
The Power of Phytochemistry

• People whose diets were highest in whole foods were the least likely to develop signs of depression by the end of 5 yr (Akbaraly et al. 2009)

• Risk of depression/anxiety disorders is 34% lower among women who ate a Traditional diet (Jacka et al, 2010)

“Traditional” Diet – Dominated by vegetables, fruit, beef, lamb, fish, and whole-grain foods

AN ABBREVIATED CARE AND FEEDING OF THE CENTRAL NERVOUS SYSTEM

This topic often skipped by Medical Schools
Orthomolecular Psychiatry

Varying the concentrations of substances normally present in the human body may control mental disease.

Linus Pauling

Discussion of optimum molecular concentrations, rates of reactions...local cerebral deficiencies may lead to mental disease...
High-dose Therapy with Ascorbate, Niacin, Folate and $B_{12}$: Pauling was Right but for the Wrong Reason

Martin L. Pall, PhD

Professor Emeritus of Biochemistry and Basic Medical Sciences, Washington State University and Research Director, The Tenth Paradigm Research Group. 638 NE 41st Ave. Portland, OR 97232-3312 USA. email: martin_pall@wsu.edu

Abstract: Pauling suggested that responses to high-dose vitamin therapy were due primarily to small increases in response due to lack of complete saturation of enzyme targets. He also suggested that they
Epinephrine (adrenalin) → Adrenochrome
Whole Foods Diet

This can’t be stressed enough!
The association between dietary patterns and mental health in early adolescence

Wendy H. Oddy \(^\text{a,*,1}\), Monique Robinson \(^\text{a,b}\), Gina L. Ambrosini \(^\text{a}\), Therese A. O’Sullivan \(^\text{a}\), Nicholas H. de Klerk \(^\text{a}\), Lawrence J. Bellin \(^\text{c}\), Sven R. Silburn \(^\text{d}\), Stephen R. Zubrick \(^\text{d}\), Fiona J. Stanley \(^\text{a}\)

**Food Intake, Diet Quality and Behavioral Problems in Children: Results from the GINI-plus/LISA-plus Studies**

Gabriele Kohlboeck \(^\text{a}\), Stefanie Sausenthaler \(^\text{a}\), Marie Stendi \(^\text{e}\), Silvye Koletzko \(^\text{b}\), Carl-Peter Baue \(^\text{a}\), Beate Schaff \(^\text{d}\)

**A Prospective Study of Diet Quality and Mental Health in Adolescents**

Felice N. Jacka \(^\text{1,2,4}\), Peter J. Kremer \(^\text{2}\), Michael Berk \(^\text{1,2,4,6}\), Andrea M. de Silva-Sanigorski \(^\text{4}\), Marjorie Moodie \(^\text{7}\), Eva R. Leslie \(^\text{8}\), Julie A. Pasco \(^\text{9}\), Boyd A. Swinburn \(^\text{9}\)

1Barwon Psychiatric Research Unit, Deakin University, Geelong, Australia, 2Department of Psychiatry, University of Melbourne, Melbourne, Australia, 3School of Psychology, Deakin University, Geelong, Australia, 4Drug and Youth Health, University of Melbourne, Melbourne, Australia, 5Mental Health Research Institute, Melbourne, Australia, 6Jack Brockhoff Child Health and Wellbeing Program, Melbourne School of Population Health, University of Melbourne, Melbourne, Australia, 7Deakin University, Geelong, Australia, 8Barwon Epidemiology and Biostatistics Unit, Deakin University, Geelong, Australia, 9WHO Collaborating Centre for Obesity Prevention, Deakin University, Geelong, Australia
Researchers found that happiness and mental health rise in an approximately dose-dependent response with the number of daily portions of fruit and vegetables… “well-being peaks at approximately 7 portions per day,”

“Our findings are consistent with the need for high levels of fruit-and-vegetable consumption for mental health and not merely for physical health.”
Spending on vegetable and fruit consumption could reduce all-cause mortality among older adults

Yuan-Ting Lo¹, Yu-Hung Chang², Mark L Wahlqvist³,⁴,⁵,⁶, Han-Bin Huang¹ and Meei-Shyuan Lee⁴,⁵*

Abstract

Background: Few studies have evaluated the linkage between food cost and mortality among older adults. This study considers the hypothesis that greater food expenditure in general, and particularly on more nutritious plant and animal-derived foods, decreases mortality in older adults.

Methods: This study uses the 1999–2000 Elderly Nutrition and Health Survey in Taiwan and follows the cohort until 2008, collecting 24-hr dietary recall data for 1781 participants (874 men and 907 women) aged 65 y or older. Using monthly mean national food prices and 24-hr recall, this study presents an estimate of daily expenditures for vegetable, fruit, animal-derived, and grain food categories. Participants were linked to the national death registry.
Gut-Brain Axis

• 35% of biopsy-proven CD cases have a history of psychiatric illness
• Patients with schizophrenia are at least three times more likely to have CD (meaning 3% of schizophrenia patients) and, if the same pattern follows, three times more likely to have GS (18% of patients).
• Odds are 33:1 that a patient with CD is unaware he/she has it.
• Nearly half of patients with CD will not manifest it yet may how psychiatric symptoms from it.
• Psychiatric manifestations will vary widely amongst CD patients.
• A gluten-free (GF) diet of CD and GS patients could eliminate or dramatically reduce psychiatric symptoms.

A Profound Adaptation...

We steep our genes daily in our dietary broth...
IMPORTANT NUTRIENTS

• Niacin (B3)
• Vitamin B6
• Folate (Vitamin B9)
• Vitamin B12
• SAM-e
• Omega 3s
• Vitamin D
• Zinc
• Calcium and Magnesium
Tryptophan
  Iron
  Calcium
  Folic Acid
  ↓
  Magnesium
  Vitamin B6
  5-HTP
  ↓
  Vitamin C
  Vitamin B6
  ↓
  Zinc
  Magnesium
  Serotonin

Tyrosine
  Folic Acid
  Iron
  Vit B6
  ↓
  L-Dopa
  ↓
  Vit B6
  Magnesium
  Dopamine
  ↓
  Vit C
  Copper
  ↓
  Noradrenaline
Experimental evidence

Germ free mice (no commensal bacteria)

- exaggerated HPA response to stress
- elevated stress hormones
- altered levels of BDNF in hippocampus
- altered levels of serotonin, noradrenaline
- increased permeability of the BBB
Human studies

• probiotics ameliorated psychological distress and reduce cortisol in healthy volunteers (Messaoudi et al. 2011)

• probiotics improved psychological symptoms in patients with chronic fatigue syndrome (Rao et al. 2009)

• fermented milk products with probiotics modulate brain activity in humans (Tillisch et al. 2013)
Lets Talk about Stress...
corticoids
26% of the observers also experienced increases in cortisol levels, even though they were not directly exposed to stress for observers who were watching loved ones go through the stressful tasks -- 40 percent experienced increased cortisol levels -- but lower for those watching a stranger -- 10 percent. The cortisol levels were still raised in 24 percent of observers when they watched through the video feed. This finding suggests that things like watching stressful moments on TV might be enough to raise cortisol levels.
The Stress Axis

Higher Brain Centers

Perception

Hypothalamus ← (−) ←

↓ CRF

Pituitary ← (−) ←

↓ ACTH

Adrenals cortisol
IMPORTANT ACTIVITIES FOR THE CNS

• Play
• Exercise
• Breathing techniques
• Mindfulness practice
• Meditation
• Yoga

Attitude!!!!
Stress Buffers
The Brain: Predictive vs Sensory Analysis

• Our brains are selected to predict what is coming
  • Much of the information we use to predict our emotional states comes from our viscera
Danziger et al. Extraneous factors in judicial decisions. *PNAS. USA* 2011 108 (17) 6889-6892
Mental illnesses are often not single diseases, but heterogenous syndromes.

Physiology and Pathophysiology is not simple, nor is diagnosis.

But ICD-10 codes are...
Depression
• Challenge serotonin hypothesis of depression – see anatomy of an epidemic
Age-standardized* percentage of adults meeting criteria for current depression

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5938a2.htm
Prevalence of current depression* among adults aged ≥20 years

http://www.cdc.gov/mmwr/preview/mmwrhtml/su6003a1.htm
Percentage of persons aged 20 and over with depression, by family income level

Past Year Prevalence of Major Depressive Episode Among U.S. Adults (2016)

Data Courtesy of SAMHSA

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### Past Year Prevalence of Major Depressive Episode Among U.S. Adolescents (2016)

Data Courtesy of SAMHSA

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Major Depressive Disorder (MDD)

Pathology:

- monoamine impairment (dysfunction in expression and receptor activity)
- lowering of monoamine production
- secondary messenger system malfunction
- cortisol excess:
  - impeding neurogenesis via reducing brain-derived neurotrophic factor
  - impaired endogenous opioid function
  - changes in GABAergic and/or glutamatergic transmission
  - cytokine or steroidal alterations
  - abnormal circadian rhythm

Major Depressive Disorder (MDD)

Many herbal medicines may have a multitude of biological effects on reuptake and receptor binding in addition to “endocrine and psychoneuroimmunological modulation”

- Inhibition of monoamine re-uptake
- Enhanced binding and sensitization of serotonin receptors
- Monoamine oxidase inhibition
- Neuroendocrine modulation
- GABAergic effects
- Cytokine modulation
- Opioid and cannabinoid system effects

Can Long-Term Treatment With Antidepressant Drugs Worsen the Course of Depression?

Giovanni A. Fava, M.D.

Background: The possibility that antidepressant drugs, while effectively treating depression, may worsen its course has received inadequate attention.

Method: A review of the literature suggesting potential depressogenic effects of long-term treatment with antidepressant drugs was performed. A MEDLINE search was conducted using the keywords tolerance, sensitization, antidepressive agents, and switching. This was supplemented by a manual search of Index Medicus under the heading “antidepressant agents” and a manual search of the literature for articles pointing to paradoxical effects of antidepressants.

Results: A number of meta-clinical finds...
The effects of detection and treatment on the outcome of major depression in primary care: a naturalistic study in 15 cities

DAVID GOLDBERG
MARTIN PRIVETT
BEDIRHAN USTUN
GREG SIMON
MICHAEL LINDEN

SUMMARY
Background. This study reports the responses of patients with confirmed depressive illnesses to different treatments in the WHO Mental Disorders in General Health Care study, conducted in 15 cities around the world.
Aim. To discover how depressions recognized by the doctor the poor prognosis of depression, measures to improve compliance with treatment would appear to be indicated.

Keywords: depression; primary care; illness recognition; naturalistic study.

Introduction
This paper examines the effects of interventions by general practitioners (GPs) in confirmed cases of depressive illness, in the 15 cities participating in the WHO Study of Mental Disorders in General Health Care. GPs have been criticized for failing to recognize depression, and, having recognized it, for failing to treat it energetically enough. However, the significance of unrecognized depression in primary care is equivocal, and studies at single centres have failed to find an association between recog-
One-Year Outcomes in WHO Screening Study for Depression

N = 740

[Bar chart showing percentages of continuing depression in different groups: Diagnosed/Antidepressants 51.6%, Diagnosed/Sedatives 44.9%, Undiagnosed/no drug 28.3%, Diagnosed/No drug 25.2%]

NIMH's Six-Year Study of Untreated Depression

Canadian Study of Risk of Long-term Disability for Depressed Workers

Serotonin?

“We propose that depressed states are high serotonin phenomena, which challenges the prominent role the low serotonin hypothesis continues to have in depression research (Albert et al., 2012). We also propose that the direct serotonin-enhancing effects of antidepressants disturb energy homeostasis and worsen symptoms. We argue that symptom reduction, which only occurs over chronic treatment, is attributable to the compensatory responses of the brain attempting to restore energy homeostasis.”
Review

Adult hippocampal neurogenesis: Is it the alpha and omega of antidepressant action?

It is now well established that all clinically available antidepressants share a common aptitude: they increase the production of adult-generated neurons in the dentate gyrus of the hippocampus. This was first observed in animal models and subsequently in human populations, highlighting the clinical relevance of this finding. Later, it was suggested
Anxiety
Mother’s Little Helper
Valium

• Brought to Market in 1963
• 1968 – 1981 best selling drug in Western World
• 1970s: 2 million people addicted, 4 x that of heroin in the 1970s
• After BDZs hit market
  • 1,028/ → 3,182/100,000 patient-care episodes
Valium

• 2014
  • 2.6% of population 18 to 35 y/o used a BDZ
  • 8.7% 65 to 80
  • Of 65 to 80 y/o, 31.4% received prescriptions for long-term use
  • In all age groups, women were about twice as likely as men to receive benzodiazepines
MOAs Sedatives & Anxiolytics

Simplistically

• Induction of neuronal depression

• Inhibition of neuronal excitation
$\text{GABA}_A$ vs $\text{GABA}_B$

Ionotropic vs Metabotropic
GABA

Several binding sites

- **GABA site**
  - Agonists
  - Antagonists

- **Barbiturate site**
  - Depressants (also ethanol?)
  - Excitants?

- **Benzodiazepine site**
  - Agonists (depressants)
  - Antagonists
  - Inverse agonists

- **Steroid site**
  - Anesthetics
  - Excitants?

- **Picrotoxin site**
  - Convulsants
  - Depressants?
GABA

• Reuptake inhibition (tiagabine)
• Increase of release (gabapentin)
• Enzymes
  • Synthesis - Glutamate decarboxylase (GAD 67)
  • Breakdown - GABA transaminase
Anxiety

Herbal MOIs

- Inducing ionic channel transmission by blockage of voltage gates
- Blockage of GABA transaminase through alteration of membrane structures (*Melissa officinalis*)
- Blockage of glutamic acid decarboxylase inhibition through alteration of membrane structures (*Matricaria recutita, Humulus lupulus*)
- Binding with benzodiazepine receptor sites, leading to increased GABA production

Acute administration of alprazolam, a benzodiazepine activating GABA receptors, inhibits cortisol secretion in patients with subclinical but not overt Cushing’s syndrome

Authors

Roberta Giordano, Rita Berardelli, Ioannis Karamouzis, Valentina D'Angelo, Andreea Picu, Clizia Zichi, Beatrice Fussotto, Maria Manzo, Giulio Mengozzi, Ezio Ghigo, Emanuela Arvat
Other Targets
Review

Chaperones and aging: role in neurodegeneration and in other civilizational diseases

Csaba Söti, Péter Csermely*

Department of Medical Chemistry, Semmelweis University, P.O. Box 260, H-1444 Budapest 8, Hungary

Received 19 September 2001; accepted 7 January 2002

Abstract

Chaperones are highly conserved proteins responsible for the preservation and repair of the correct conformation of cellular macromolecules, such as proteins, RNAs, etc. Environmental stress leads to chaperone (heat-shock protein, stress protein) induction reflecting the protective role of chaperones as a key factor for cell survival and in repairing cellular damage after stress. The present review summarizes our current knowledge about the chaperone-deficiency in the aging process, as well as the possible involvement of chaperones in neurodegenerative diseases, such as in Alzheimer’s, Parkinson’s, Huntington- and prion-related diseases. We also summarize
Chaperones in Neurological Diseases

- Impaired signaling
- Aging
- Complexes of damaged proteins with chaperones
- Disorganized cytoarchitecture
- Silent mutations exposed by chaperone overload
- Cytoplasmic chaperones
Cytokines

Sickness Behavior
Sickness Behavior

Defined as anxiety, anhedonia, social withdrawal, fatigue, and sleep disturbances
Sickness Behavior

Proinflammatory mediators have been shown to induce anxiety, anhedonia, social withdrawal, fatigue, and sleep disturbances, defined as “sickness behavior”

Sickness Behavior

Systemic administration of proinflammatory agents is able to promote the activation of microglial cells in the hippocampus and stimulate the release of proinflammatory cytokines in the CNS.


Activation of microglial cells in the hippocampus and the subsequent release of proinflammatory cytokines in the CNS is associated with depression and anxiety.


Sickness Behavior

Central administration of IL-1β & TNF-α cytokines induces sickness behavior in animals

Sickness Behavior

Inflammation appears to be part of the etiology in the pathophysiology of different psychiatric syndromes, including major depression.


Elevated biomarkers of systemic inflammation, as C-reactive protein, have been associated with depressive symptoms.

Sickness Behavior

Depressed patients show higher peripheral blood levels of proinflammatory cytokines

Sickness Behavior

Elevated inflammatory markers predict reduced response to antidepressant treatment

Sickness Behavior

Increased prevalence of depression has been observed in patients with autoimmune disorders

Blocking cytokine signaling can exert beneficial effects on mood

Sickness Behavior

Post-mortem studies in patients with major depression evidenced that also the innate immune response is altered, possibly contributing to the pathogenesis of depression.

Hypothesis

The efficacy of different psychoactive treatments may be mediated by immunomodulatory properties

Perspectives

What is the primary substrate of the universe?
The Beginning

Matter $\rightarrow$ Consciousness
The Beginning

Matter ← Consciousness
The Endocannabinoid System

This is not necessarily about Cannabis but about basic physiology
Endocannabinoid Basics

• CB1 and CB2 receptors found throughout the body
• Anandamide (AEA) and 2-AG synthesized on-demand for homeostatic functions
• Enzymes to synthesize AEA & 2-AG
• Enzymes to metabolize AEA & 2-AG
CB1 Receptor Distribution in Human Brain

Endogenous Cannabinoid Ligands: The Endocannabinoids

Anandamide (AEA)
Devane, Mechoulam et al., 1992

2-arachidonoylglycerol (2-AG)
Mechoulam et al., 1995
Sugiura et al., 1995
Endogenous Cannabinoid Ligands: The Endocannabinoids

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG):

• Retrograde messengers in nervous system.

• Autocrine or paracrine mediators elsewhere.

• Synthesized “on demand” from cell membrane precursors (arachidonic acid derivatives) and immediately released.

• Degraded by enzymatic hydrolysis
  • AEA -> fatty acid amide hydrolase (FAAH)
  • 2-AG -> monoacylglycerol lipase (MAGL)

(McPartland, 2008)
Numerous Other Endogenous Cannabinoids

Kogan 2006
Other Endocannabinoid Targets

• GPR55 (Ryberg, 2007; Staton, 2008)

• TRPV1 “capsaicin receptor” (Ross, 2003)

• PPARs: Peroxisome proliferator-activated receptors (O'sullivan, 2007)

• Voltage-gated ion channels
  • Ca2+, Na+, and various types of K+ channels

• Ligand-gated ion channels
  • 5-HT3 and nicotinic ACh receptors (Oz, 2006)
The Endocannabinoid System Function and Regulates the:

- Nervous System
- Connective Tissues
- Immune System
- Neoplasms
- Embryology
- Digestive System
- Hunger and Feeding
Endocannabinoid System
Increasing Resilience

Neuroplastic effects such as synaptic plasticity, neurogenesis and neurotrophin expression in the hippocampus are modulated by endogenous cannabinoids.


Keys to Resilience

A range of human genes and polymorphisms associated with

- Neuropeptide Y
- Noradrenergic systems
- Dopaminergic systems
- Serotonergic systems
- Brain Derived Neurotropic Factor
- Hypothalamus-Pituitary-Adrenal axis

have been linked to resilience

Chronic stress leads to epigenetic dysregulation in the neuropeptide-Y and cannabinoid CB1 receptor genes in the mouse cingulate cortex

Ermelinda Lomazzo, Florian König, Leila Abassi, Ruth Jelinek, Beat Lutz

Abstract

Persistent stress triggers a variety of mechanisms, which may ultimately lead to the occurrence of anxiety- and depression-related disorders. Epigenetic modifications...
Cannabinoid type 2 receptors in dopamine neurons inhibits psychomotor behaviors, alters anxiety, depression and alcohol preference


Cannabinoid CB2 receptors (CB2Rs) are expressed in mouse brain dopamine (DA) neurons and are...
Regulation of noradrenergic and serotonergic systems by cannabinoids: relevance to cannabinoid-induced effects

Aitziber Mendiguren, Erik Aostri, Joseba Pineda

Abstract

The cannabinoid system is composed of Gi/o protein-coupled cannabinoid type 1 receptor (CB₁) and cannabinoid type 2 (CB₂) receptor and endogenous compounds. The CB₁ receptor is widely distributed in the central nervous system (CNS) and it is
Cannabidiol Induces Rapid and Sustained Antidepressant-Like Effects Through Increased BDNF Signaling and Synaptogenesis in the Prefrontal Cortex

Amanda J. Sales, Manoela V. Fogaça, Ariandra G. Sartim, Vitor S. Pereira, Gregers Wegener, Francisco S. Guimarães, Sâmia R. L. Joca

Received: 19 January 2018 / Accepted: 22 May 2018
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Abstract
Currently available antidepressants have a substantial time lag to induce therapeutic response and a relatively low efficacy. The development of drugs that addresses these limitations is critical to improving public health. Cannabidiol (CBD), a non-psychotomimetic component of *Cannabis sativa*, is a promising compound since it shows large-
CRH causes a reduction in the endocannabinoid anandamide within the amygdala. We found that CRH signaling in the amygdala promotes an anxious phenotype that is prevented by FAAH inhibition. CRH signaling coordinates a disruption of tonic AEA activity to promote a state of anxiety.
Several lines of evidence suggest that facilitation of cannabinoid signaling within the hippocampus brain region prevents stress-induced behavioral changes.
The Anxiolytic Potential and Psychotropic Side Effects of an *Echinacea* Preparation in Laboratory Animals and Healthy Volunteers

József Haller,¹ Tamás F. Freund,¹ Katalin Gyimesi Pelczer,¹ János Füredi,² Laszlo Krecsak³ and János Zámbori²

¹Institute of Experimental Medicine, Budapest, Hungary
²Mensana 2004 Psychiatry Clinic, Budapest, Hungary
³Eotvos Lorand University, Budapest, Hungary

We investigated the toxicity, psychotropic side effects and anxiolytic potential of an *Echinacea angustifolia* extract that produced promising effects in laboratory tests performed earlier. Rats were studied in the elevated plus-maze, forced swim test and alteredcorsa. Volunteers were given 400 mg of the extract three times a day for 7 days.
there is reduced FAAH expression associated with a FAAH SNP that decreases anxiety-like behaviors
Knock-in mice that biologically recapitulate a common human mutation in the gene for...

(a) Self-report trait anxiety (STAI)

(b) % Time in open arm
At the End of the Day

The Endocannabinoid System as a fundamental system overlapping with many other key systems alters our perception, the way we move through the world and our physiological tone
Physiological Order

- Cardiovascular System
- Neuro-Immuno-Endocrine
- Gut-Brain Axis
- Endocannabinoid System
Questions?

kevin@phytochemks.com