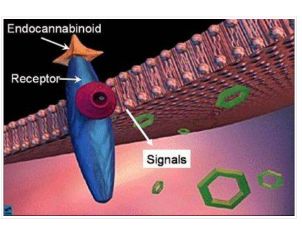
List of Linkable Endocannabiniods & Cannabis Science & Research

Overview

The ECS is thought to connect the physical and emotional responses to stress with appetite and energy regulation. It is thought to affect a wide variety of physiologic processes including nociception (pain sense), motor control, memory and learning, appetite, food intake, and energy balance.



Short (3min) VIDEOS

- How Cannabis Works
- Exploring the Endocannabinoid System
- Obisity and the Endocannabinoid System (ECS)
- Holistic Biochemistry of Cannabinoids, by Robert Melamede, PhD
- Cancer Cure - Cannabis & Cannabinoids,by Robert Melamede, PhD
- Cannabis Memory PTSD (Post Traumatic Stress Disorder)

Science and Research

1. **Updated Definition ~** Cannabinoids Encyclopedia Entry.
2. **Updated ~** Cannabinoid Receptor Ligands.
3. **1986 - Study ~** Cellular effects of cannabinoids.
4. **1990 - Study ~** Cannabinoid Receptor Localization in Brain.
5. **1991 - Study ~** Molecular cloning of a human cannabinoid receptor which is also expressed in testis.
6. **1993 - Study ~** Loss of cannabinoid receptors in the substantia nigra in Huntington's disease.
7. **1993 - Study ~** Molecular characterization of a peripheral receptor for cannabinoids.
8. **1997 - Study ~** Brain Chemicals Mimic Marijuana.
9. **1998 - Study ~** Changes in cannabinoid receptor binding and mRNA levels in several brain regions of aged rats.
10. **1998 - Study ~** Body's 'cannabis' could hold blood pressure key.
11. 1999 - Study ~ Pain modulation by release of the endogenous cannabinoid anandamide.
12. 1999 - Study ~ Cannabis and cannabinoids: pharmacology and rationale for clinical use.
13. 1999 - Study ~ Finding of the endocannabinoid signalling system in Hydra, a very primitive organism: possible role in the feeding response.
14. 1999 - News ~ Links found between marijuana and vision.
15. 1999 - News ~ Why your brain is primed for a high.
16. 2000 - Study ~ The Cannabinoid System and Cytokine Network.
17. 2000 - Study ~ Endocannabinoids and Vascular Function.
18. 2000 - Study ~ Cannabinoids, immune system and cytokine network.
19. 2000 - Study ~ Endogenous cannabinoids and appetite.
20. 2001 - Study ~ Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation.
21. 2001 - Study ~ Control by the endogenous cannabinoid system of ras oncogene-dependent tumor growth.
22. 2001 - Study ~ The cannabinoids: an overview. Therapeutic implications in vomiting and nausea after cancer chemotherapy, in appetite promotion, in multiple sclerosis and in neuroprotection.
23. 2001 - News ~ How Marijuana Works.
24. 2001 - News ~ Healing Haze?
25. 2001 - News ~ Attack of the munchies.
26. 2002 - Study ~ Targeting the endocannabinoid system in cancer therapy: A call for further research.
27. 2002 - Study ~ International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors.
28. 2002 - Study ~ Sourcing the Code: Searching for the Evolutionary Origins of Cannabinoid Receptors, Vanilloid Receptors, and Anandamide.
29. 2002 - Study ~ Cannabinoid receptors and their ligands.
30. 2002 - Study ~ Activation of cannabinoid receptors decreases the area of ischemic myocardial necrosis.
31. 2002 - Study ~ Cannabinoids and multiple sclerosis.
32. 2002 - Study ~ The endogenous cannabinoid system controls extinction of aversive memories.
33. 2003 - Study - Cannabinoids inhibit neurodegeneration in models of multiple sclerosis
34. 2003 - Study ~ Manipulation of the endocannabinoid system by a general anaesthetic.
35. 2003 - Study ~ The Endocannabinoid System in Human Keratinocytes.
36. 2003 - Study ~ The cannabinoid system and immune modulation.
37. 2003 - Study ~ The Endogenous Cannabinoid System Regulates Seizure Frequency and Duration in a Model of Temporal Lobe Epilepsy.
38. 2003 - Study ~ Endogenous cannabinoid system as a modulator of food intake.
39. 2003 - Study ~ Cannabis and the brain.
40. 2003 - Study ~ The cannabinoid system: a role in both the homeostatic and hedonic control of eating?
41. 2003 - Study ~ The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis.
42. 2003 - Study ~ Vasodilator actions of abnormal-cannabidiol in rat isolated small mesenteric artery.
43. 2003 - Study ~ Therapeutic potential of cannabinoids in CNS disease.
44. 2003 - Study ~ The endocannabinoid system and Huntington's disease.
45. 2003 - Study ~ Effect of maternal under-nutrition on pup body weight and hypothalamic endocannabinoid levels.
46. 2004 - Study ~ The endocannabinoid system: a general view and latest additions.
47. 2004 - Study ~ Effects of Cannabis Therapy on Endogenous Cannabinoids.
48. 2004 - Study ~ The endogenous cannabinoid system protects against colonic inflammation.
49. 2004 - Study ~ The endocannabinoid system: physiology and pharmacology.
50. 2004 - Study ~ Involvement of cannabinoid receptors in gut motility and visceral perception.
51. 2004 - Study ~ Fibromyalgia, IBS, and the Endocannabinoid-CB-Receptor (ECBR) system.
52. 2004 - Study - Clinical Endocannabinoid Deficiency.
53. 2004 - Study - The endogenous cannabinoid system protects against colonic inflammation.
54. 2005 - Study ~ The endocannabinoid system drives neural progenitor proliferation.
55. 2005 - Study ~ Enhancing Cannabinoid Neurotransmission Augments the Extinction of Conditioned Fear.
56. 2005 - Study ~ Activation of the Peripheral Endocannabinoid System in Human Obesity.
57. 2005 - Study ~ Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood.
58. 2005 - Study ~ Regulation of bone mass, bone loss and osteoclast activity by cannabinoid receptors.
59. 2005 - Study ~ The endocannabinoid system: Physiology and pharmacology.
60. 2005 - Study ~ Evidence that the plant cannabinoid Δ9-tetrahydrocannabivarin is a cannabinoid CB1 and CB2 receptor antagonist.
61. 2005 - Study ~ Blood pressure regulation by endocannabinoids and their receptors.
62. 2005 - Study ~ Decreased endocannabinoid levels in the brain and beneficial effects of agents activating cannabinoid and/or vanilloid receptors in a rat model of multiple sclerosis.
63. 2005 - Study ~ The Endogenous Cannabinoid System. Therapeutic Implications for Neurologic and Psychiatric Disorders.
64. 2005 - Study ~ The cannabinoid system and its importance in the perinatal period.
65. 2005 - Study ~ New Antidepressant Drug Increases 'Brain's Own Cannabis'
66. 2005 - Study ~ Role of cannabinoid receptors in alcohol abuse.
67. 2005 - Study ~ Marijuana May Grow Neurons in the Brain.
68. 2005 - Study - The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase 2.
69. 2005 - Study - Harm reduction - The cannabis paradox.
70. 2006 - Study - Endocannabinoids: Multi-scaled, Global Homeostatic Regulators of Cells and Society.
71. 2006 - Study - The Endocannabinoid System as an Emerging Target of Pharmacotherapy.
72. 2006 - Study ~ Agonists of cannabinoid receptor 1 and 2 inhibit experimental colitis induced by oil of mustard and by dextran sulfate sodium.
73. 2006 - Study ~ Experimental autoimmune encephalomyelitis disrupts endocannabinoid-mediated neuroprotection.
74. 2006 - Study ~ Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mi.
75. 2006 - Study ~ Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes.
76. 2006 - Study ~ Inhibition of Salivary Secretion by Activation of Cannabinoid Receptors.
77. 2006 - Study ~ Cannabinoids and the Endocannabinoid System.
78. 2006 - Study ~ Cannabinoids biology: the search for new therapeutic targets.
79. 2006 - Study ~ Activation of G-proteins in brain by endogenous and exogenous cannabinoids.
80. 2006 - Study ~ Cannabinoid receptors and endocannabinoids: evidence for new players.
81. 2006 - Study ~ The emerging role of the endocannabinoid system in endocrine regulation and energy balance.
82. 2006 - Study ~ Experimental autoimmune encephalomyelitis disrupts endocannabinoid-mediated neuroprotection.
83. 2006 - Study ~ Neurophysiological, Neuroimmunological, and Neuroendocrine Basis of Pruritus.
84. 2006 - Study ~ The Endocannabinoid System as an Emerging Target of Pharmacotherapy.
85. 2006 - Study ~ Not Too Excited? Thank Your Endocannabinoids.
86. 2006 - Study ~ Cannabinoids and the Endocannabinoid System.
87. 2006 - Study ~ Endocannabinoid overactivity and intestinal inflammation.
88. 2006 - Study ~ The Endocannabinoid System Controls Key Epileptogenic Circuits in the Hippocampus.
89. 2006 - Study ~ Cannabinoid receptors and endocannabinoids: evidence for new players.
90. 2006 - Study ~ Endocannabinoids in Chronic Migraine: CSF Findings Suggest a System Failure.
91. 2006 - Study ~ Frontiers in pruritus research: scratching the brain for more effective itch therapy.
92. 2006 - Study ~ Dysregulation of the Peripheral and Adipose Tissue Endocannabinoid System in Human Abdominal Obesity.
93. 2006 - Study ~ Endocannabinoids and the gastrointestinal tract.
94. 2006 - Study ~ Evolutionary Origins of the Endocannabinoid System.
95. 2006 - Study ~ Neuromodulatory functions of the endocannabinoid system.
96. 2007 - Study ~ The endocannabinoid system is dysregulated in multiple sclerosis.
97. 2007 - News - Migraine may be related to under production of cannabinoids.
98. 2007 - Study ~ Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro.
99. 2007 - Study ~ Increased endocannabinoid levels reduce the development of precancerous lesions in the mouse colon.
100. 2007 - Study ~ Endocannabinoids block status epilepticus in cultured hippocampal neurons.
101. 2007 - Study ~ Activation of cannabinoid CB1 and CB2 receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats.
102. 2007 - Study ~ The psychoactive plant cannabinoid, Delta9-tetrahydrocannabinol, is antagonized by Delta8- and Delta9-tetrahydrocannabivarin in mice in vivo.
103. 2007 - Study ~ Downregulation of the CB1 Cannabinoid Receptor and Related Molecular Elements of the Endocannabinoid System in Epileptic Human Hippocampus.
104. 2007 - Study ~ Expression and function of cannabinoid receptors CB1 and CB2 and their cognate cannabinoid ligands in murine embryonic stem cells.
105. 2007 - Study ~ Cannabinoids: A New Group of Agonists of PPARs.
106. 2007 - Study ~ Endocannabinoid metabolism and uptake: novel targets for neuropathic and inflammatory pain.
107. 2007 - Study ~ Endocannabinoids and the gastrointestinal tract: what are the key questions?
108. 2007 - Study ~ The endocannabinoid system is dysregulated in multiple sclerosis.
109. 2007 - Study ~ Neuropharmacology of the endocannabinoid signaling system-molecular mechanisms, biological actions and synaptic plasticity.
110. 2007 - Study ~ Cannabinoid action in the olfactory epithelium.
111. 2007 - Study ~ A possible role for the endocannabinoid system in the neurobiology of depression.
112. 2007 - Study ~ The complications of promiscuity: endocannabinoid action and metabolism.
113. 2007 - Study ~ Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors.
114. 2007 - Study ~ The CB1 Cannabinoid Receptor Mediates Excitotoxicity-induced Neural Progenitor Proliferation and Neurogenesis.
115. 2007 - Study ~ Modulation of Fear and Anxiety by the Endogenous Cannabinoid System.
116. 2007 - Study ~ The endocannabinoid system in targeting inflammatory neurodegenerative diseases.
117. 2007 - Study ~ A possible role for the endocannabinoid system in the neurobiology of depression.
118. 2007 - Study ~ Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward.
119. 2007 - Study ~ Modulation of the endocannabinoid system: therapeutic potential against cocaine dependence.
120. 2007 - Study ~ Increased endocannabinoid levels reduce the development of precancerous lesions in the mouse colon.
121. 2007 - Study ~ Cannabis and Endocannabinoids: The Old Man and the Teenagers.
122. 2007 - Study ~ Endocannabinoids, cannabinoid receptors and inflammatory stress: an interview with Dr. Pál Pacher.
123. 2007 - Study ~ The endocannabinoid system and neurogenesis in health and disease.
124. 2007 - Study ~ Endocannabinoid metabolism and uptake: novel targets for neuropathic and inflammatory pain.
125. 2007 - Study ~ Cannabinoids and neuroprotection in motor-related disorders.
126. 2007 - Study ~ The (Endo)Cannabinoid System in Multiple Sclerosis and Amyotrophic Lateral Sclerosis.
127. 2007 - Study ~ Expression of cannabinoid receptors and neurotrophins in human gliomas.
128. 2007 - Study ~ The endocannabinoid network: insight into the regulation of the neuroendocrine and metabolic systems.
129. 2007 - Study ~ Overactivity of the intestinal endocannabinoid system in celiac disease and in methotrexate-treated rats.
130. 2007 - News ~ The endocannabinoid system.
131. 2007 - News ~ The importance of the endocannabinoid-system.
132. 2007 - News ~ Endocannabinoids appear to play important role in regulating inflammation.
133. 2008 - Study - The role of endocannabinoid system in physiological and pathological processes in the eye.
134. 2008 - Study - Endocannabinoids in the retina: From marijuana to neuroprotection.
135. 2008 - Study ~ Cannabinoid receptors in acute and chronic complications of atherosclerosis.
136. 2008 - Study ~ Endocannabinoid Dysregulation in the Pancreas and Adipose Tissue of Mice Fed With a High-fat Diet.
137. 2008 - Study ~ Attenuation of Allergic Contact Dermatitis Through the Endocannabinoid System.
138. 2008 - Study ~ Cannabinoids Inhibit HIV-1 Gp120-Mediated Insults in Brain Microvascular Endothelial Cells.
139. 2008 - Study ~ Genetic variation in endocannabinoid metabolism, gastrointestinal motility, and sensation.
140. 2008 - Study ~ Multiple sclerosis, cannabinoids, and cognition.
141. 2008 - Study ~ The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin.
142. 2008 - Study ~ Cannabinoid CB2 receptors in human brain inflammation.
143. 2008 - Study ~ Endocannabinoids and the Control of Energy Homeostasis.
144. 2008 - Study ~ Cannabinoid receptors and the regulation of bone mass.
145. 2008 - Study ~ Function of cannabinoids in heart failure.
146. 2008 - Study ~ Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis.
147. 2008 - Study ~ The endocannabinoid system: an osteopathic perspective.
148. 2008 - Study ~ Modulation of the Endocannabinoid System in Cardiovascular Disease.
149. 2008 - Study ~ Endocannabinoid Dysregulation in the Pancreas and Adipose Tissue of Mice Fed With a High-fat Diet.
150. 2008 - Study ~ The Medicinal Chemistry of Agents Targeting the Endogenous Cannabinoid System.
151. 2008 - Study ~ Gender-dependent increases with healthy aging of the human cerebral cannabinoid-type 1 receptor binding using [(18)F]MK-9470 PET.
152. 2008 - Study ~ The rat pineal gland comprises an endocannabinoid system.
153. 2008 - Study ~ The endocannabinoid system in Huntington's disease.
154. 2008 - Study ~ The endocannabinoid system in amyotrophic lateral sclerosis.
155. 2008 - Study ~ Expression of the endocannabinoid system in fibroblasts and myofascial tissues.
156. 2008 - Study ~ Activation of the endocannabinoid system by organophosphorus nerve agents.
157. **2008 - Study ~** The endocannabinoid system: emotion, learning and addiction.
158. **2008 - Study ~** Immunomodulatory lipids in plants: plant fatty acid amides and the human endocannabinoid system.
159. **2008 - Study ~** Endocannabinoids and the neurochemistry of gluttony.
160. **2008 - Study ~** Immunomodulatory lipids in plants: plant fatty acid amides and the human endocannabinoid system.
161. **2008 - Study ~** Endocannabinoids and the neurochemistry of gluttony.
162. **2008 - Study ~** Endogenous cannabinoids: structure and metabolism.
163. **2008 - Study ~** Biology of endocannabinoid synthesis system.
164. **2008 - Study ~** The endocannabinoid system and multiple sclerosis.
165. **2008 - Study ~** Cannabinoid receptors: where they are and what they do.
166. **2008 - Study ~** Dysregulation of the endocannabinoid system in obesity.
167. **2008 - Study ~** The role of endocannabinoid system in physiological and pathological processes in the eye.

Science and Research

1. **Study - 2009 ~ The endocannabinoid system and Pregnancy: Emphasis during development**
2. **Study -** 2013 ~ Apr;226(4):781-92 **Cannabidiol enhances consolidation of explicit fear extinction in humans.**
3. Study - 2005 Nov 1; 115(11): 3104–3116. **Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects**
4. **2008 - Study ~** The endocannabinoid system: emotion, learning and addiction.
5. **2008 - News ~** New brain cells implicated in machinery of cannabinoid signaling.
6. **2008 - News ~** Starting Point Of Sun-Induced Skin Cancer Discovered: Molecular 'Hooks' Also Pull Compounds From Marijuana From Bloodstream.
7. **2008 - News ~** Salutary pizza spice.
8. **2009 - Study -** Parasitic brain infection, endocannabinoids, and schizophrenia.
9. **2009 - Study -** Endocannabinoid chemical biology: a tool for the development of novel therapies.
10. **2009 - Study -** Endocannabinoid System: An overview of its potential in current medical practice
11. **2009 - Study -** The endocannabinoid system as a target for the treatment of motor dysfunction
12. 2009 - Study ~ Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation.
13. 2009 - Study ~ Changes in the Endocannabinoid System May Give Insight into new and Effective Treatments for Cancer.
14. 2009 - Study ~ Effects of Cannabinoids on Caffeine Contractures in Slow and Fast Skeletal Muscle Fibers of the Frog.
15. 2009 - Study ~ Ulcerative Colitis Induces Changes on the Expression of the Endocannabinoid System in the Human Colonic Tissue.
16. 2009 - Study ~ Localisation and Function of the Endocannabinoid System in the Human Ovary.
17. 2009 - Study ~ Voluntary Exercise and Sucrose Consumption Enhance Cannabinoid CB1 Receptor Sensitivity in the Striatum.
18. 2009 - Study ~ Cannabinoids: An emerging role in pain management?
19. 2009 - Study ~ Dynamic regulation of the endocannabinoid system: implications for analgesia.
20. 2009 - Study ~ Endocannabinoid signalling as an anti-inflammatory therapeutic target in atherosclerosis: does it work?
21. 2009 - Study ~ Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation.
22. 2009 - Study ~ Biomarkers of Endocannabinoid System Activation in Severe Obesity.
23. 2009 - Study ~ The emerging role of the endocannabinoid system in cardiovascular disease.
24. 2009 - Study ~ Endocannabinoid signaling in microglial cells.
25. 2009 - Study ~ Endocannabinoid-mediated control of synaptic transmission.
26. 2009 - Study ~ The endocannabinoid system and pain.
27. 2009 - Study ~ The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities.
28. 2009 - Study ~ Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress.
29. 2009 - Ariticle ~ Cannabinoids, Miracle Drug of the 21st Century by Jeffrey Dach MD.
30. 2009 - Study ~ Impairments in Endocannabinoid Signaling and Depressive Illness.
31. 2009 - Editorial ~ The Endocannabinoid System in the Brain: From Biology to Therapy.
32. 2009 - Study ~ The endocannabinoid system: an ancient signaling involved in the control of male fertility.
33. 2009 - Study ~ Cannabinoid receptors in brain: pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications.
34. 2009 - Study ~ Bidirectional regulation of novelty-induced behavioral inhibition by the endocannabinoid system.
35. 2009 - Study ~ Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder.
36. 2009 - Study ~ An examination of anthocyanins' and anthocyanidins' affinity for cannabinoid receptors.
37. 2009 - Study ~ Post-ischemic brain damage: the endocannabinoid system in the mechanisms of neuronal death.
38. 2009 - Study ~ The endocannabinoid system: Its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation.
39. 2009 - Study ~ Cannabinoid receptors: a brief history and "what's hot".
40. 2009 - Study ~ An introduction to the endocannabinoid system: from the early to the latest concepts.
41. 2009 - Study ~ The endocannabinoid system as a target for the treatment of motor dysfunction.
42. 2009 - Study ~ Endocannabinoid System: An overview of its potential in current medical practice.
43. 2009 - Study ~ From endocannabinoid profiling to 'endocannabinoid therapeutics'.
44. 2009 - Study ~ Cannabinoid receptors in brain: pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications.
45. 2009 - News ~ Enhanced Sweet Taste: Endocannabinoids Act Directly on Tongue Taste Receptors.
46. 2009 - News ~ The cannabinoid system: cannabinoids and receptors.
47. 2009 - News ~ Enhanced sweet taste: This is your tongue on pot.
48. 2010 - Study ~ Endocannabinoid Overload.
49. 2010 - Study ~ Motion Sickness, Stress and the Endocannabinoid System.
50. 2010 - Study ~ The endocannabinoid system as a target for the treatment of neurodegenerative disease.
51. 2010 - Study ~ Enhancement of endocannabinoid signaling by fatty acid amide hydrolase inhibition: a neuroprotective therapeutic modality.
52. 2010 - Study ~ Endocannabinoids selectively enhance sweet taste.
53. 2010 - Study ~ The endocannabinoid system links gut microbiota to adipogenesis.
54. 2010 - Study ~ Evidence for a Role of Endocannabinoids, Astrocytes and p38 Phosphorylation in the Resolution of Postoperative Pain.
55. 2010 - Study ~ The multiple functions of the endocannabinoid system: a focus on the regulation of food intake.
56. 2010 - Study ~ Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression.
57. 2010 - Study ~ Endocannabinoid signalling: has it got rhythm?
58. 2010 - Study ~ Dietary docosahexaenoic acid supplementation alters select physiological endocannabinoid-system metabolites in brain and plasma.
59. 2010 - Study ~ Functional role of cannabinoid receptors in urinary bladder.
60. 2010 - Study ~ International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2.
61. 2010 - Study ~ The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors.
62. 2010 - Study ~ Mice lacking cannabinoid CB1-, CB2-receptors or both receptors show increased susceptibility to trinitrobenzene sulfonic acid (TNBS)-induced colitis.
63. 2010 - Study ~ Rehashing endocannabinoid antagonists: can we selectively target the periphery to safely treat obesity and type 2 diabetes?
64. 2010 - Study ~ Involvement of cannabinoid-1 and cannabinoid-2 receptors in septic ileus.
65. 2010 - Study ~ Potential role of the cannabinoid receptor CB in the pathogenesis of erosive and non-erosive gastro-oesophageal reflux disease.
66. 2010 - Study ~ Bimodal control of stimulated food intake by the endocannabinoid system.
67. 2010 - Study ~ The endocannabinoid system modulates the valence of the emotion associated to food ingestion.
68. 2010 - Study ~ Substantially altered expression pattern of cannabinoid receptor 2 and activated endocannabinoid system in patients with severe heart failure.
69. 2010 - Study ~ Deficiency in Endocannabinoid Signaling in the Nucleus Accumbens Induced by Chronic Unpredictable Stress.
70. 2010 - Study ~ Opposite changes in cannabinoid CB1 and CB2 receptor expression in human gliomas.
71. 2010 - Study ~ Can autism be triggered by acetaminophen activation of the endocannabinoid system?
72. 2010 - Study ~ Targeting the Endocannabinoid System for the Treatment of Cancer - A Practical View.
73. 2010 - Study ~ Alterations of the endocannabinoid system in an animal model of migraine: Evaluation in cerebral areas of rat.
74. 2010 - Study ~ Recent advances in the understanding of the role of the endocannabinoid system in liver diseases.
75. 2010 - Study ~ The endocannabinoid system in the inflammatory and neurodegenerative processes of multiple sclerosis and of amyotrophic lateral sclerosis.
76. 2010 - Study ~ The Multiplicity of Action of Cannabinoids: Implications for Treating Neurodegeneration.
77. 2010 - Study ~ The endocannabinoid signaling system: a marriage of PUFA and musculoskeletal health.
78. 2010 - Study ~ Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels.
79. 2010 - News ~ Not Feeling Well? Perhaps You're 'Marijuana Deficient'.
80. 2010 - News ~ Levels And Efficacy Of A Marijuana-Like Substance In The Brain Controlled By Newly Discovered Mechanism.
81. 2011 - Study ~ Gadolinium-HU-308-incorporated micelles.
82. 2011 - Study ~ Gut feelings about the endocannabinoid system.
83. 2011- Study ~ Cannabinoid system and cyclooxygenases inhibitors.
84. 2011 - Study ~ The endocannabinoid system and cancer: therapeutic implication.
85. 2011 - Study ~ Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis.
86. 2011 - Study ~ Endocannabinoid system protects against cryptogenic seizures.
87. 2011 - Study ~ The endocannabinoid system in sepsis – a potential target to improve microcirculation?
88. 2011 - Study ~ Endocannabinoid system in cardiovascular disorders - new pharmacotherapeutic opportunities.
89. 2011 - Study ~ Role for cannabinoid receptors in human proximal tubular hypertrophy.
90. 2011 - Study ~ The G protein-coupled cannabinoid-1 (CB(1)) receptor of mammalian brain: Inhibition by phthalate esters in vitro.
91. 2011 - Study ~ Update on the endocannabinoid system as an anticancer target.
92. 2011 - Study ~ The endocannabinoid system in the regulation of emotions throughout lifespan: a discussion on therapeutic perspectives.
93. 2011 - Study ~ Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions.
94. 2011 - Study ~ A study on the endogenous cannabinoid system synthetic and catabolic enzyme levels in patients with obstructive sleep apnea.
95. 2011 - Study ~ Molecular reorganization of endocannabinoid signalling in Alzheimer's disease.
96. 2011 - Study ~ Homeostatic changes of the endocannabinoid system in Parkinson's disease.
97. 2011 - Study ~ The endocannabinoid system and cancer: therapeutic implication.
98. 2011 - Study ~ The endocannabinoid system in prostate cancer.
99. 2011 - Study ~ Effect of capacitation on the endocannabinoid system of mouse sperm.
100. 2011 - Study ~ The highs and lows of cannabinoid receptor expression in disease: mechanisms and their therapeutic implications.
101. 2011 - Study ~ Early exposure to Environmental enrichment alters the expression of genes of the endocannabinoid system.
102. 2011 - Study ~ Endocannabinoid signaling in the amygdala: anatomy, synaptic signaling, behavior, and adaptations to stress.
103. 2011 - Study ~ Effects of exercise stress on the endocannabinoid system in humans under field conditions.
104. 2011 - Study ~ α-Tocopherol and α-tocopheryl phosphate interact with the cannabinoid system in the rodent hippocampus.
105. 2011 - Study ~ Alternative targets within the endocannabinoid system for future treatment of gastrointestinal diseases.
106. 2011 - Study ~ Cannabis sativa and the endogenous cannabinoid system: therapeutic potential for appetite regulation.
107. 2011 - Study ~ Endocannabinoid system dysfunction in mood and related disorders.
108. 2011 - Study ~ Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects.
109. 2011 - Study ~ Interictal Type 1 Cannabinoid Receptor Binding is Increased in Female Migraine Patients.
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111. 2011 - Study ~ The Endocannabinoid System: Plant-Derived Cannabinoids in Diabetes and Diabetic Complications.
112. 2011 - Study ~ Effects of endocannabinoid system modulation on cognitive and emotional behavior.
113. 2011 - Study ~ Endogenous cannabinoid system regulates intestinal barrier function in vivo through cannabinoid type 1 receptor activation.
114. 2011 - Study ~ The genetic basis of the endocannabinoid system and drug addiction in humans.
115. 2011 - Study ~ Inhibition of basal and ultraviolet B-induced melanogenesis by cannabinoid CB(1) receptors: a keratinocyte-dependent effect.
116. 2011 - News ~ Omega-3 deficiency disrupts cannibinoid receptor function in brain.
117. 2011 - News ~ A Brain Wrought Without Omega-3.
118. 2011 - News ~ Introduction to the Endocannabinoid System.
119. 2011 - News ~ Marijuana Compound Treats Multiple Health Issues.
120. 2011 - News ~ Pot and Pumpkin Pie: Endocannabinoid System Enhanced by Vitamin E.
121. 2011 - News ~ Poor Diet Impairs Cannabinoid Receptors.
122. 2011 - News ~ Chocolate & marijuana: chemical cousins.
123. 2011 - News ~ Binge Eating May Be a High All Its Own.
124. 2011 - News ~ Research provides new clues to understand link between deficits of AGPO-3, depression.
125. 2012 - Study ~ Irritable bowel syndrome: a dysfunction of the endocannabinoid system?
126. 2012 - Study ~ Endocannabinoids Stimulate Human Melanogenesis via Type-1 Cannabinoid Receptor.
127. 2012 - Study ~ Site-specific and time-dependent activation of the endocannabinoid system after transection of long-range projections.
128. 2012 - Study ~ Extinction learning of rewards in the rat: is there a role for CB1 receptors?
129. 2012 - Study ~ The CB(1) Receptor-Mediated Endocannabinoid Signaling and NGF: The Novel Targets of Curcumin.
130. 2012 - Study ~ Cannabinoid modulation of noradrenergic circuits: Implications for psychiatric disorders.
131. 2012 - Study ~ Endocannabinoids at the synapse a decade after the Dies Mirabilis (29 March 2001): what we still do not know.
132. 2012 - Study ~ The endocannabinoid system: a revolving plate in neuro-immune interaction in health and disease.
133. 2012 - Study ~ Cannabinoid signalling regulates inflammation and energy balance: The importance of the brain-gut axis.
134. 2012 - Study ~ Minireview: endocannabinoids and gonadal hormones: bidirectional interactions in physiology and behavior.
135. 2012 - Study ~ Alteration of endocannabinoid system in human gliomas.
136. 2012 - Study ~ Expression and localization of the cannabinoid receptor type 1 and the enzyme fatty acid amide hydrolase in the retina of vervet monkeys.
137. 2012 - Study ~ Regulation of endocannabinoid release by G proteins: A paracrine mechanism of G protein-coupled receptor action.
138. 2012 - Study ~ Cannabinoid receptors: nomenclature and pharmacological principles.
139. 2012 - Study ~ The Role of Cannabinoids In Inflammatory Modulation of Allergic Respiratory Disorders, Inflammatory Pain and Ischemic Stroke.
140. 2012 - Study ~ Sex differences in cannabinoid receptor-1 (CB1) pharmacology in mice selectively bred for high voluntary wheel-running behavior.
141. 2012 - Study ~ Role of Lipid Rafts/Caveolae in the Anticancer Effect of Endocannabinoids.
142. 2012 - Study ~ Circulating Endocannabinoid Concentrations and Sexual Arousal in Women.
143. 2012 - Study ~ A current overview of cannabinoids and glucocorticoids in facilitating extinction of aversive memories: Potential extinction enhancers.
144. 2012 - Study ~ Cannabinoid Receptors CB1 and CB2 Form Functional Heteromers in Brain.
145. 2012 - Study ~ The co-expression of the endocannabinoid system and the rankérankl signalling pathway in human bone and asteoclast culture.
146. 2012 - Study ~ Acute Reduction of Anandamide-Hydrolase (FAAH) Activity is Coupled With a Reduction of Nociceptive Pathways Facilitation in Medication-Overuse Headache Subjects After Withdrawal Treatment.
147. 2012 - Study ~ Potential Control of Multiple Sclerosis by Cannabis and the Endocannabinoid System.
148. 2012 - Study ~ The role of the endocannabinoid system in eating disorders: pharmacological implications.
149. **2012 - Study ~** Sex differences in cannabinoid pharmacology: A reflection of differences in the endocannabinoid system?
150. **2012 - Study ~** Nutritional n-3 polyunsaturated fatty acids deficiency alters cannabinoid receptor signaling pathway in the brain and associated anxiety-like behavior in mice.
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156. **2012 - News ~** Cannabinoid 2 receptors regulate impulsive behavior.
157. **2012 - News ~** 'Runner's High' may have played role in evolutionary history of humans.

Introduction to the endocannabinoid system

ABSTRACT / intro

Biomedical research on cannabis began in earnest in the latter part of the last century primarily because of the prevalence of overweight and obesity in both adults and children. Knowledge of the ECS may lead to better treatment for cardiovascular disease and type 2 diabetes associated with being overweight.

The ECS is a complex endogenous signaling system (produced by the brain) comprised of Cannabinoid receptors (CB1 and CB2), Endocannabinoid ligands, and proteins that are involved with endocannabinoid synthesis. Endocannabinoid receptors are found mostly in the brain, but also in tissues, glands such as the liver, gastrointestinal tract and skeletal muscles.

Pharmaceutical companies are primarily interested in the inactivity mode of the ECS receptors.

The ECS is thought to connect the physical and emotional responses to stress with appetite and energy regulation. It is thought to affect a wide variety of physiologic processes including nociception (pain sense), motor control, memory and learning, appetite, food intake, and energy balance

Cannabis and Cannabinoids, (D 9-tetrahydrocannabinol),

CBD (cannabidiol) and CBN (cannabinol).

Cannabis contains a number of cannabinoids, of which the most abundant are THC (D 9-tetrahydrocannabinol), CBD (cannabidiol) and CBN (cannabinol). The active ingredient, which gets you high, is THC. In the plant, CBD is a precursor and CBN a metabolite of THC. As cannabis gets older, THC gradually breaks down to CBN.

THC is the substance found to have most psychoactive effect, and also the most effect on symptoms such as pain or bronchospasm. CBN and CBD are not psychoactive themselves; however CBD can take the edge off a THC high, tending to relax the user rather than increasing anxiety and paranoia.

CBD has also been found to have anticonvulsant properties (potential value in treating epilepsy, MS, muscle spasms etc), and recently published research has indicated CBD to be effective in reducing neurotoxic brain damage following strokes or head trauma.

The proposed mechanism of action also suggests CBD may offer some protection against ecstasy-derived neurotoxicity (long-term depletion of serotonergic receptors), although this has not specifically been investigated. CBD is normally present in significant quantities in hashish (cannabis resin), although in most herbal cannabis or "skunk" the levels of CBD are usually low or absent.

Although smoked cannabis offers some advantages over oral preparations (rapid onset of action, ability to control dose), the smoke contains carcinogens, tars and other lung irritants which may cause respiratory diseases and lung cancer.

The lack of an effective filter in "roaches" and the deep inhalation techniques used by cannabis smokers increases this risk. However the study of smoke composition quoted by the BMA and others referred to poor quality herbal cannabis smoked "neat", and the relevance of these results to tobacco/hash spliffs or high-THC varieties is questionable. At least one pharmaceutical company is developing alternative quick-acting delivery systems for plant-derived cannabinoid combinations, avoiding the need for smoking.

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Back to Top

Introduction

Endocannabinoid Synthesis & Release In standard neurotransmission, the pre-synaptic neuron releases neurotransmitter into the synaptic cleft which binds to cognate receptors expressed on the post-synaptic neuron. Upon binding, the neuron depolarizes.

This depolarization facilitates the influx of calcium into the neuron; this increase in calcium activates an enzyme called transacylase which catalyzes the first step of endocannabinoid biosynthesis by converting phosphatidylethanolamine, a membrane-resident phospholipid, into N-acyl-phosphatidylethanolamine (NAPE).

Experiments have shown that multiple phospholipases cleave NAPE to yield anandamide. In NAPE-phospholipase D (NAPEPLD) knockouts, the PLD-mediated cleavage of NAPE is reduced, not abolished, in low calcium concentrations, suggesting multiple, distinct pathways are involved in Anandamide biosynthesis (Leung et al., 2006). Once released into the extracellular space by a putative endocannabinoid transporter, messengers are vulnerable to glial inactivation.

Endocannabinoids are uptaken via a putative transporter and degraded by fatty acid amide hydrolase (FAAH) which cleaves anandamide and MGLL, which cleaves 2-AG to arachidonic acid & ethanolamine and arachidonic acid & glycerol, respectively (reviewed in Pazos et al., 2005). While arachidonic acid is a substrate for leukotriene and prostaglandin synthesis, it is unclear whether this degradative byproduct has novel functions in the CNS (Yamaguchi et al., 2001; Brock, T., 2005).

Emerging data in the field also points to FAAH being expressed in the postsynaptic neuron, suggesting it also contributes to the clearance and inactivation of anandamide and 2-AG by endocannabinoid reuptake.

Endocannabinoid Binding & Signal Transduction While there have been some papers that have linked concurrent stimulation of dopamine and CB1 receptors to an acute rise in cAMP production, it is accepted that CB1 activation causes an inhibition of cyclic adenosine monophosphate (or cAMP) when activated alone.

This inhibition of cAMP is followed by phosphorylation and subsequent activation of not only a suite of MAP kinases but also the PI3/PKB and MEK/ERK pathway (Galve-Roperh et al., 2002; Davis et al., 2005; Jones et al., 2005; Graham et al., 2006).

Results from rat hippocampal gene chip data after acute administration of tetrahydrocannabinol showed an increase in the expression of myelin basic protein, endoplasmic proteins, cytochrome oxidase, and two cell adhesion molecules: NCAM, and SC1; decreases in expression were seen in both calmodulin and ribosomal RNAs (Kittler et al., 2000).

In addition, CB1 activation has been demonstrated to increase the activity of transcription factors like c-Fos and Krox-24 (Graham et al., 2006).

Endocannabinoid Binding & Alterations in Neuronal Excitability The molecular mechanisms of CB1-mediated changes to the membrane voltage have also been studied in detail. CB1 agonists reduce calcium influx by blocking the activity of voltage-dependent N-, P/Q- and L-type calcium channels.

In addition to acting on calcium channels, Gi/o and Gs, subunits of G protein-coupled receptors, activation has also been shown to modulate potassium channel activity. Recent studies have found that CB1 activation facilitates GIRK, a potassium channel belonging to the Kir3 family.

Corroborating Guo and Ikeda, Binzen et al. performed a series of immunohistochemistry experiments that demonstrated CB1 co-localized with GIRK and Kv1.4 potassium channels, suggesting that these two may interact in physiological contexts.

In the central nervous system, CB1 receptors, for the most part, influence neuronal excitability indirectly, by reducing the impact of incoming synaptic input.

This mechanism ("presynaptic inhibition") is believed to occur when a neuron ("postsynaptic") releases endocannabinoids in a retrograde fashion, binding to CB1 receptors expressed on nerve terminals of an input neuron ("presynaptic").

CB1 receptors then reduce the amount of neurotransmitter released, so that subsequent input from the presynaptic neuron has less of an impact on the postsynaptic neuron. It is likely that presynaptic inhibition uses many of the same ion channel mechanisms listed above, although recent evidence has shown that CB1 receptors can also regulate neurotransmitter release by a non-ion channel mechanism, i.e. through Gi/o mediated inhibition of adenylyl cyclase and Protein Kinase A.

Still, direct effects of CB1 receptors on membrane excitability have been reported, and strongly impact the firing of cortical neurons In a series of behavioral experiments, Palazzo et al. demonstrated that NMDA, an ionotropic glutamate receptor, and the metabotropic glutamate receptors (mGluRs) work in concert with CB1 to induce analgesia in mice, although the mechanism underlying this effect is unclear.

Together, these findings suggest that CB1 influences neuronal excitability by a variety of mechanisms, and these effects are relevant to perception and behavior.

CB1 -/- Phenotype Neuroscientists often utilize transgenic CB1 knockout mice (i.e. the mice have had the gene encoding the CB1 receptor deleted or removed) to discern novel roles for the ECS. While CB1 knockout mice are healthy and live into adulthood, there are some differences among mice without CB1 and wild-type (i.e. "normal" mice with the receptor intact);

When under a high-fat diet CB1 knockout mice tend to be about sixty percent leaner and slightly less hungry than wildtype.

Compared to wildtype, CB1 knockout mice exhibit severe deficits in motor learning, memory retrieval, and increased difficulty in completing the Morris water maze.

There is also evidence indicating that these knockout animals have an increased incidence and severity of stroke and seizure (Parmentier et al., 2002; Marsicano et al., 2003).

Memory Mice treated with tetrahydrocannabinol show suppression of long-term potentiation in the hippocampus - a process that is essential for the formation and storage of long-term memory. These results concur with anecdotal evidence suggesting

that is essential for the formation and storage of long-term memory. These results concur with anecdotal evidence suggesting that smoked preparations of *Cannabis* attenuates short-term memory. Indeed, mice without the CB1 receptor show enhanced memory and long-term potentiation indicating that the endocannabinoid system may play a pivotal role in the extinction of old memories.
Recent research reported in a 2005 *Journal Of Clinical Investigation* article indicate that the high-dose treatment of rats with the synthetic cannabinoid, HU-210 over a period of a few weeks resulted in stimulation of neural growth in the rats' hippocampus region, a part of the limbic system playing a part in the formation of declarative and spatial memories.

Appetite Emerging data suggests that THC acts via CB1 receptors on hypothalamic nuclei, thus directly increasing appetite. It is thought that hypothalamic neurons tonically produce endocannabinoids that work to tightly regulate hunger.
The amount of endocannabinoids produced is inversely correlated with the amount of leptin in the blood. For example, mice without leptin not only become massively obese but have higher-than-normal levels of hypothalamic endocannabinoids.
Similarly, when these mice were treated with an endocannabinoid antagonist, such as Rimonabant, food intake was reduced.
When the CB1 receptor is knocked out in mice, these animals tend to be leaner and less hungry than wild-type (or "normal") mice. While there is need for more research, these results (and others) suggest that exogenous cannabinoids (as from smoking marijuana) in the hypothalamus activates a pathway responsible for food-seeking behavior.
Sweet taste receptors are found in the intestine and pancreas, where they help regulate nutrient absorption, insulin secretion and energy metabolism.
If endocannibinoids also modulate the responses of pancreatic and intestinal sweet receptors, the findings may open doors to the development of novel therapeutic compounds to combat metabolic diseases such as obesity and diabetes.
Monell Chemical Senses Center (2009, December 23). Enhanced sweet taste: Endocannabinoids act directly on tongue taste receptors.
ECS and Multiple Sclerosis Historical records from ancient China and Greece suggest that preparations of *Cannabis Indica* were commonly prescribed to ameliorate multiple sclerosis-like symptoms such as tremors and muscle pain; unfortunately, however, treatment with marinol hasn't shown the same efficacy as inhaled Cannabis.
Due to the illegality of Cannabis and rising incidence of multiple sclerosis patients who self-medicate with the drug, there has been much interest in exploiting the endocannabinoid system in the cerebellum to provide a legal and effective relief.
In mouse models of multiple sclerosis, there is a profound reduction and reorganization of CB1 receptors in the cerebellum (Cabranes et al., 2006). Serial sections of cerebellar tissue subjected to immunohistochemistry revealed that this aberrant expression occurred during the relapse phase but returned to normal during the remitting phase of the disease (Cabranes et al., 2006).
There is recent data indicating that CB1 agonists promote the *in vitro* survival of oligodendrocytes, specialized support glia that are involved in axonal myelination, in the absence of growth and trophic factors; in addition, these agonist have been shown to promote mRNA expression of myelin lipid protein. (Kittler et al., 2000; Mollna-Holgado et al., 2002).
Taken together, these studies point to the exciting possibility that cannabinoid treatment may not only be able to attenuate the symptoms of multiple sclerosis but also improve oligodendrocyte function (reviewed in Pertwee, 2001; Mollna-Holgado et al., 2002). 2-arachidonylglycerol stimulates proliferation of a microglial cell line by a CB_2 receptor dependent mechanism, and the number of microglial cells is increased in multiple sclerosis.
Role in Human Female Reproduction The developing embryo expresses cannabinoid receptors early in development that are responsive to anandamide which is secreted in the uterus.
This signaling is important in regulating the timing of embryonic implantation and uterine receptivity.
In mice, it has been shown that anandamide modulates the probability of implantation to the uterine wall. For example, in humans, the likelihood of miscarriage increases if uterine anandamide levels are too high or low.
These results suggest that proper intake of exogenous cannabinoids (e.g. marijuana) can decrease the likelihood for pregnancy for women with high anandamide levels, and alternatively, it can increase the likelihood for pregnancy in women whose anandamide levels were too low. More...
Role in Hippocampal Neurogenesis In the adult brain, the endocannabinoid system facilitates neurogenesis ("birth of new neurons") of hippocampal granule cells.
In the subgranular zone of the dentate gyrus, multipotent neural progenitors (NP) give rise to daughter cells that, over the course of several weeks, mature into granule cells whose axons project to and synapse onto dendrites on the CA3 region.
Very recent data suggests that the maturing granule cells are dependent on a reelin, a molecular guidance cue, for proper migration through the dentate gyrus (Gong et al., 2007). NPs in the hippocampus have been shown to possess FAAH and express CB1 and utilize 2-AG.
Intriguingly, CB1 activation by endogenous or exogenous promote NP proliferation and differentiation; this activation is absent in CB1 knockouts and abolished in the presence ofantagonist.

Top Home

Clinical Endocannabinoid Deficiency

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Neuroendocrinol Lett 2004; 25(1/2):31–39 NEL251204R02
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Abstract
OBJECTIVES: This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis.

METHODS:
Available literature was reviewed, and literature searches pursuedvia the National Library of Medicine database and other resources.

RESULTS:
Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT1A and inhibits 5-HT2A receptors supporting therapeutic efficacy in acute and preventive migraine treatment.

Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine
generator.
THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging.

CONCLUSION: Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.

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Top Home

The endocannabinoid system is dysregulated in multiple sclerosis

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- Received December 22, 2006.
- Revision received May 10, 2007.
- Accepted June 14, 2007.

Summary
The ability of cannabinoids to modulate both inflammatory and degenerative neuronal damage prompted investigations on the potential benefits of such compounds in multiple sclerosis (MS) and in animal models of this disorder.
Here we measured endocannabinoid levels, metabolism and binding, and physiological activities in 26 patients with MS (17 females, aged 19–43 years), 25 healthy controls and in mice with experimental autoimmune encephalomyelitis (EAE), a preclinical model of MS.
Our results show that MS and EAE are associated with significant alterations of the endocannabinoid system.
We found that anandamide (AEA), but not 2-arachidonoylglycerol (2-AG), was increased in the CSF of relapsing MS patients. AEA concentrations were also higher in peripheral lymphocytes of these patients, an effect associated with increased synthesis and reduced degradation of this endocannabinoid. Increased synthesis, reduced degradation, and increased levels of AEA were also detected in the brains of EAE mice in the acute phase of the disease, possibly accounting for its anti-excitotoxic action in this disorder.
Accordingly, neurophysiological recordings from single neurons confirmed that excitatory transmission in EAE slices is inhibited by CB1 receptor activation, while inhibitory transmission is not. Our study suggests that targeting the endocannabinoid system might be useful for the treatment of MS.
IntroductionImmune-mediated attack of oligodendrocytes and myelin sheaths is a primary pathological event in multiple sclerosis (MS). Neurodegenerative damage, however, occurs early in this disorder, paralleling inflammation ...**read more**

Top Home

Cannabinoids inhibit neurodegeneration in models of multiple sclerosis

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- Received February 19, 2003.
- Revision received April 23, 2003.
- Accepted April 28, 2003.

Summary
Multiple sclerosis is increasingly being recognized as a neurodegenerative disease that is triggered by inflammatory attack of the CNS. As yet there is no satisfactory treatment. Using experimental allergic encephalo myelitis (EAE), an animal model of multiple sclerosis, we demonstrate that the cannabinoid system is neuroprotective during EAE.
Mice deficient in the cannabinoid receptor CB_1 tolerate inflammatory and excito toxic insults poorly and develop substantial neurodegeneration following immune attack in EAE.
In addition, exogenous CB_1 agonists can provide significant neuroprotection from the consequences of inflammatory CNS disease in an experimental allergic uveitis model.
Therefore, in addition to symptom management, cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in multiple sclerosis and probably other diseases...**read more**

Top Home

Migraine may be related to under production of cannabinoids Last Updated Sunday, 30 December 2007

Perugia, Italy:
Patients with a history of migraine headaches may be suffering from a clinical deficiency of the endocannabinoid system, according to clinical trial data published in the European Journal of Clinical Pharmacology.

Investigators at Italy's University of Perugia, Department of Public Health, reported that patients with chronic migrainespossessed "significantly lower" levels of the endogenous cannabinoids anandamide and 2-arachidonylglycerol (2-AG) in
their platelets compared to age-matched controls.

"These data support the potential involvement of a dysfunctioning of the endocannabinoid and serotonergic systems in the pathology of chronic migraine and medication-overuse headaches," researchers' concluded.

A previous paper published in the journal Neuroendocrinology Letters similarly suggested that migraine, fibromyalgia, and other treatment-resistant conditions may be associated with dysfunctions in the endocannabinoid system.This system is believed to play a primary role in regulating humans' mood, appetite, skeletal development, motor coordination, digestion, and reproduction.
Full text of the study: "Endocannabinoids in platelets of chronic migraine patients and medication-overuse headache patients: relation with serotonin levels," **European Journal of Clinical Pharmacology**, **November 2007:**

http://www.springerlink.com/content/672084122072449x/
Anandamide: http://en.wikipedia.org/wiki/Anandamide
"The Endocannabinoid System: Physiology and Pharmacology" :
http://alcalc.oxfordjournals.org/cgi/content/full/40/1/2

"Clinical Endocannabinoid Deficiency (CECD): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?"
http://www.immunesupport.com/library/showarticle.cfm/ID/5710/

Top Home

Endocannabinoids: Multi-scaled, Global Homeostatic Regulators of Cells and Society
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Endocannabinoids: Multi-scaled, Global Homeostatic Regulators of Cells and Society

Abstract
Living systems are far from equilibrium open systems that exhibit many scales of emergent behavior.
They may be abstractly viewed as a complex weave of dissipative structures that maintain organization by passing electrons from reduced hydrocarbons to oxygen. Free radicals are unavoidable byproducts of biological electron flow.
Due to their highly reactive chemical properties, free radicals modify all classes of biological molecules (carbohydrates, lipids, nucleic acids, and proteins).
As a result, free radicals are destructive, however, they also have critical adaptive properties. The disruptive nature of free radicals makes them the "friction of life".
They are believed to be the etiological agents behind age related illnesses such as cardiovascular, immunological, and neurological diseases, cancer, and ageing itself.
Endocannabinoids are marijuana-like compounds that have their origins hundreds of millions of years in the evolutionary past.
They serve as fundamental modulators of energy homeostasis in many multi-celled organisms including all vertebrates. They have widespread biological activities that may often be attributed to their ability to minimize the negative consequences of free radicals. In fact, since cannabinoids (endo and exo) possess many anti-aging properties, they may be viewed as the "oil of life".
The biological effects of cannabinoids transcend many scales of organization. Cannabinoids regulate sub-cellular biochemistry, intercellular communication, and metabolism involving all biological systems (cardiovascular, digestive, excretory, immunological, nervous, musculo-skeletal, reproductive and tegumentary).
It is proposed that their emergent properties extend to social, political, and economic phenomena. As a result of man's unprecedented impact on his surroundings, the selective pressure on the evolutionary progression of man's endocannabinoid system has novel time constraints that may be best met by behavioral modification.
Presently, mankind is engaged in an evolutionary battle between more primitive members of a relatively cannabinoid deficient population and those relatively more endowed. The outcome of this genetic conflict may determine man's survival.

Top Home

Endocannabinoid chemical biology: a tool for the development of novel therapies
Petrosino S, Ligresti A, Di Marzo V
[JOURNAL ARTICLE]
Curr Opin Chem Biol 2009 May 18.
The identification of the major psychoactive constituent of Cannabis and marijuana, Delta(9)-tetrahydrocannabinol, opened the way first to the cloning of the G-protein-coupled cannabinoid CB(1) and CB(2) receptors, and then to the isolation and characterisation of their endogenous agonists, the endocannabinoids.
Considerable progress has been made in the characterisation of pathways and enzymes for the biosynthesis and degradation of anandamide and 2-arachidonoylglycerol, the two best-known endocannabinoids, as well as of endocannabinoid-related molecules, such as the N-acylethanolamines, which, as in the case of N-palmitoylethanolamine and N-oleoylethanolamine, may interact with other receptor types.
However, it is still not fully understood how other plant cannabinoids, of which cannabidiol is the most studied representative, exert their pharmacological effects.

Together with these issues, this first review article on the endocannabinoids describes the synthetic pharmacological tools that have been designed so far to interact with the proteins of the 'endocannabinoid system' and that can potentially be used as templates for the development of new therapies.

Top Home

Harm reduction - the cannabis paradox

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Bioenergetics Institute, 1420 Austin Bluffs Parkway, University of Colorado, Colorado Springs, 80918, USA
- *Harm Reduction Journal* 2005
- The electronic version of this article is the complete one and can be found online at:
http://www.harmreductionjournal.com/content/2/1/17

Received:19 November 2004
Accepted:22 September 2005
Published:22 September 2005© 2005 Melamede;
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AbstractThis article examines harm reduction from a novel perspective. Its central thesis is that harm reduction is not only a social concept, but also a biological one. More specifically, evolution does not make moral distinctions in the selection process, but utilizes a cannabis-based approach to harm reduction in order to promote survival of the fittest.
- Evidence will be provided from peer-reviewed scientific literature that supports the hypothesis that humans, and all animals, make and use internally produced cannabis-like products (endocannabinoids) as part of the evolutionary harm reduction program. More specifically, endocannabinoids homeostatically regulate all body systems (cardiovascular, digestive, endocrine, excretory, immune, nervous, musculo-skeletal, reproductive). Therefore, the health of each individual is dependant on this system working appropriately.
IntroductionThe concept of harm reduction is at the heart of conflicting international drug policies. The Dutch pioneered this approach. Today most European countries and Canada have embraced the idea that society benefits most when drug policy is designed to help people with drug problems to live better lives rather than to punish them.
- In contrast, the United States federal policy demands rigid zero tolerance with overwhelming emphasis on incarceration of offenders (the Drug War). Although, seemingly reasonable arguments can be made to support both sides of the dispute, the recent global trend towards harm reduction has resulted from the acknowledgement that drug use has been a part of all societies throughout history and the realization that repressive policies are expensive, ineffective, and often harmful.
A dramatic example of the benefits that can result from a harm reduction approach to drugs is seen with needle exchange programs.
- While prohibitionists argue that providing clean injection equipment promotes drug use, the facts do not support this contention. For example, the Australian needle exchange program is credited with keeping the HIV/AIDS infection rate very much lower than what is typically found globally http://www.chr.asn.au/about/harmreduction webcite. Commonly cited examples of the failed repressive policies championed by the United States are the now repealed alcohol prohibition and the current drug war.
- Crime, financial support for terrorism, disrespect for the law, and destruction of families, communities, and ecosystems can all be attributed to drug prohibition. Yet, the staggering cost of the drug war, driven by United States policy and taxpayers' money, amounts to many billions of dollars a year.
Cannabis is the third most commonly used drug in the world, following tobacco and alcohol. In the United States, much of the drug war is focused on marijuana (over 700,000 people arrested last year alone). Is there justification for this policy?

- The gateway theory states marijuana use leads to the use of other drugs, and drives the U.S. policy despite evidence that suggests alcohol and tobacco use may foster the gateway effect....**read entire article (large)**

Top Home

Endocannabinoids in the retina: From marijuana to neuroprotection
Yazulla S
Endocannabinoids in the retina: From marijuana to neuroprotection. [JOURNAL ARTICLE]
Prog Retin Eye Res 2008 Aug 3.
The active component of the marijuana plant Cannabis sativa, Delta(9)-tetrahydrocannabinol (THC), produces numerous beneficial effects, including analgesia, appetite stimulation and nausea reduction, in addition to its psychotropic effects.
THC mimics the action of endogenous fatty acid derivatives, referred to as endocannabinoids. The effects of THC and the endocannabinoids are mediated largely by metabotropic receptors that are distributed throughout the nervous and peripheral organ systems.
There is great interest in endocannabinoids for their role in neuroplasticity as well as for therapeutic use in numerous conditions, including pain, stroke, cancer, obesity, osteoporosis, fertility, neurodegenerative diseases, multiple sclerosis, glaucoma and inflammatory diseases, among others.
However, there has been relatively far less research on this topic in the eye and retina compared with the brain and other organ systems.
The purpose of this review is to introduce the "cannabinergic" field to the retinal community. All of the fundamental works on cannabinoids have been performed in non-retinal preparations, necessitating extensive dependence on this literature for background.
Happily, the retinal cannabinoid system has much in common with other regions of the central nervous system.
For example, there is general agreement that cannabinoids suppress dopamine release and presynaptically reduce transmitter release from cones and bipolar cells. How these effects relate to light and dark adaptations, receptive field formation, temporal properties of ganglion cells or visual perception are unknown.
The presence of multiple endocannabinoids, degradative enzymes with their bioactive metabolites, and receptors provides a broad spectrum of opportunities for basic research and to identify targets for therapeutic application to retinal diseases.

Top Home

Parasitic brain infection, endocannabinoids, and schizophrenia
Melamede R
[Journal Article]
Med Hypotheses 2009 Feb; 72(2):220-2.
Cannabis use has often been associated with various forms of psychosis. Today it is well established that everyone produces marijuana-like compounds known as endocannabinoids.
The endocannabinoid system is a homeostatic regulator of all body systems including the nervous system.
As a result, imbalances in the endocannabinoid system have been considered as possible causes of various forms of mental illness and abnormal behavior.
In this paper, a novel hypothesis is presented that suggests that an as yet undefined subset of schizophrenia is caused by an excess of endocannabinoids that are produced to protect the brain in response to infections by agents such as Toxoplasma gondii.

Top Home

The role of endocannabinoid system in physiological and pathological processes in the eye
Nadolska K, Goś R
Abstract, Journal Article]
Klin Oczna 2008; 110(10-12):392-6.
Plant of Cannabis sativa/ marihuana except for its psychotropic effects possesses a range of pharmacological properties, that has been utilized for medical purposes over a period of millenia. Investigations concerning biochemical mechanism of action of the main and most active pharmacological compound of Cannabis sativa, cannabinoid 9-THC, contributed to the discovery of cannabinoid receptors both in the central nervous system (CNS) and peripheral tissues, that mediated actions of this substance.
The discovery made possible identification of a new, endogenous signaling system reffered to as the endocannabinoid system.
Besides cannabinoid receptors CB1 and CB2, the system includes it's endogenic ligands (endocannabinoids) and compounds that participate in their biosynthesis and inactivation. Structure and functioning of the endocannabinoid system is conservative in all vertebrates.
It's activation with plant, synthetic and endogenous cannabinoids has an influence on multiple physiological and pathological processes within the eye.

Top Home

The Endocannabinoid System as an Emerging Target of Pharmacotherapy

PHARMACOLOGICAL REVIEWS Vol. 58, No. 3
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Abstract
The recent identification of cannabinoid receptors and their endogenous lipid ligands has triggered an exponential growth of studies exploring the endocannabinoid system and its regulatory functions in health and disease.

Such studies have been greatly facilitated by the introduction of selective cannabinoid receptor antagonists and inhibitors of endocannabinoid metabolism and transport, as well as mice deficient in cannabinoid receptors or the endocannabinoid-degrading enzyme fatty acid amidohydrolase.
In the past decade, the endocannabinoid system has been implicated in a growing number of physiological functions, both in the central and peripheral nervous systems and in peripheral organs.
More importantly, modulating the activity of the endocannabinoid system turned out to hold therapeutic promise in a wide range of disparate diseases and pathological conditions, ranging from mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's disease, neuropathic pain, multiple sclerosis and spinal cord injury, to cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, and osteoporosis, to name just a few.

An impediment to the development of cannabinoid medications has been the socially unacceptable psychoactive properties of plant-derived or synthetic agonists, mediated by CB1
receptors.

However, this problem does not arise when the therapeutic aim is achieved by treatment with a

CB1 receptor antagonist, such as in obesity, and may also be absent when the action of endocannabinoids is enhanced indirectly through blocking their metabolism
or transport.

The use of selective CB2 receptor agonists, which lack psychoactive properties, could represent another promising avenue for certain conditions. The abuse potential of plant-derived cannabinoids may also be limited through the use of preparations with controlled composition and the careful selection of dose and route of administration.

The growing number of preclinical studies and clinical trials with compounds that modulate the endocannabinoid system will probably result in novel therapeutic approaches in a number of diseases for which current treatments do not fully address the patients' need. Here, we provide a comprehensive overview on the current state of knowledge of the endocannabinoid system as a target of pharmacotherapy... **full pdf article**

Top Home
Endocannabinoid System: An overview of its potential in current medical practice
Mouslech Z, Valla V
Endocannabinoid system: An overview of its potential in current medical practice. [Journal Article, Review]
Neuro Endocrinol Lett 2009; 30(2):153-79.
The endocannabinoid system (ECS) is a lipid signalling system, comprising of the endogenous cannabis-like ligands (endocannabinoids) anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which derive from arachidonic acid.
These bind to a family of G-protein-coupled receptors, called CB1 and CB2. The cannabinoid receptor 1 (CB1R) is distributed in brain areas associated with motor control, emotional responses, motivated behaviour and energy homeostasis.
In the periphery, the same receptor is expressed in the adipose tissue, pancreas, liver, GI tract, skeletal muscles, heart and the reproduction system. The CB2R is mainly expressed in the immune system regulating its functions.
Endocannabinoids are synthesized and released upon demand in a receptor-dependent way. They act as retrograde signalling messengers in GABAergic and glutamatergic synapses and as modulators of postsynaptic transmission, interacting with other neurotransmitters.
Endocannabinoids are transported into cells by a specific uptake system and degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). The ECS is involved in various pathophysiological conditions in central and peripheral tissues.
It is implicated in the hormonal regulation of food intake, cardiovascular, gastrointestinal, immune, behavioral, antiproliferative and mammalian reproduction functions.
Recent advances have correlated the ECS with drug addiction and alcoholism.
The growing number of preclinical and clinical data on ECS modulators is bound to result in novel therapeutic approaches for a number of diseases currently treated inadequately. The ECS dysregulation has been correlated to obesity and metabolic syndrome pathogenesis. Rimonabant is the first CB1 blocker launched to treat cardiometabolic risk factors in obese and overweight patients. Phase III clinical trials showed the drug's ability to regulate intra-abdominal fat tissue levels, lipidemic, glycemic and inflammatory parameters.
However, safety conerns have led to its withrawal. The role of endocannabinoids in mammalian reproduction is an emerging research area given their implication in fertilization, preimplantation embryo and spermatogenesis. The relevant preclinical data on endocannabinoid signalling open up new perspectives as a target to improve infertility and reproductive health in humans.
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The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase 2Copyright © Copyright 2005 by Gut

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Revised June 24, 2005; Accepted July 5, 2005.
This article has been cited by other articles in PMC.

Abstract
Background and aims: Cyclooxygenase 2 (COX-2) is upregulated in most colorectal cancers and is responsible for metabolism of the endogenous cannabinoid, anandamide, into prostaglandin-ethanolamides (PG-EAs).

The aims of this study were to determine whether anandamide and PG-EAs induce cell death in colorectal carcinoma (CRC) cells, and whether high levels of COX-2 in CRC cells could be utilised for their specific targeting for cell death by anandamide.

Methods: We determined the effect of anandamide on human CRC cell growth by measuring cell growth and cell death, whether this was dependent on COX-2 protein expression or enzyme activity, and the potential involvement of PG-EAs in induction of cell death.

Results: Anandamide inhibited the growth of CRC cell lines HT29 and HCA7/C29 (moderate and high COX-2 expressors, respectively) but had little effect on the very low COX-2 expressing CRC cell line, SW480. Induction of cell death in HT29 and HCA7/C29 cell lines was partially rescued by the COX-2 selective inhibitor NS398. Cell death induced by anandamide was neither apoptosis nor necrosis.

Furthermore, inhibition of fatty acid amide hydrolase potentiated the non-apoptotic cell death, indicating that anandamide induced cell death was mediated via metabolism of anandamide by COX-2, rather than its degradation into arachidonic acid and ethanolamine. Interestingly, both PGE_2-EA and PGD_2-EA induced classical apoptosis.

Conclusions: These findings suggest anandamide may be a useful chemopreventive/therapeutic agent for colorectal cancer as it targets cells that are high expressors of COX-2, and may also be used in the eradication of tumour cells that have become resistant to apoptosis.
Keywords: cannabinoid, anandamide, colorectal carcinoma, cyclooxygenase-2, fatty acid amide hydrolase, cell death

- Other Sections▼
  - Abstract
  - METHODOLOGY
  - RESULTS
  - DISCUSSION
  - REFERENCES

Colorectal cancer is one of the major causes of cancer death in the industrialised world, and the incidence is likely to rise even further with the increasing trend towards obesity. Therefore, it is essential to develop more prevention strategies and novel agents for colorectal cancer chemotherapy.

Recently, there has been a great deal of interest in cannabinoids as novel anticancer agents... **read full text**

The endogenous cannabinoid system protects against colonic inflammation

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The endogenous cannabinoid system protects against colonic inflammation

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Received July 11, 2003; Accepted February 3, 2004.
This article has been cited by other articles in PMC.

- Other Sections▼
  - Abstract
  - Introduction
  - Methods
  - Results
  - Discussion
  - References

Abstract
Excessive inflammatory responses can emerge as a potential danger for organisms' health.

Physiological balance between pro- and anti-inflammatory processes constitutes an important feature of responses against harmful events. Here, we show that cannabinoid receptors type 1 (CB1) mediate intrinsic protective signals that counteract proinflammatory responses.

Both intrarectal infusion of 2,4-dinitrobenzene sulfonic acid (DNBS) and oral administration of dextrane sulfate sodium induced stronger inflammation in CB1-deficient mice (*CB1*$^{-/-}$) than in wild-type littermates (*CB1*$^{+/+}$).

Treatment of wild-type mice with the specific CB1 antagonist *N*-(piperidino-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide (SR141716A) mimicked the phenotype of *CB1*$^{-/-}$ mice, showing an acute requirement of CB1 receptors for protection from inflammation.

Consistently, treatment with the cannabinoid receptor agonist *R*(-)-7-hydroxy-Δ_6-tetra-hydrocannabinol-dimethylheptyl (HU210) or genetic ablation of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) resulted in protection against DNBS-induced colitis.

Electrophysiological recordings from circular smooth muscle cells, performed 8 hours after DNBS treatment, revealed spontaneous oscillatory action potentials in *CB1*$^{-/-}$ but not in *CB1*$^{+/+}$ colons, indicating an early CB1-mediated control of inflammation-induced irritation of smooth muscle cells. DNBS treatment increased the percentage of myenteric neurons expressing CB1 receptors, suggesting an enhancement of cannabinoid signaling during colitis.

Our results indicate that the endogenous cannabinoid system represents a promising therapeutic target for the treatment of intestinal disease conditions characterized by excessive inflammatory responses.

IntroductionColon pathologies span a wide range of different conditions, including frankly inflammatory bowel diseases (ulcerative colitis and Crohn disease) and so-called functional bowel diseases (e.g., irritable bowel syndrome), and represent an important and widespread health problem in modern society... **read full study**

The endocannabinoid system as a target for the treatment of motor dysfunctionBr J Pharmacol. 2009 Apr;156(7):1029-40. Epub 2009 Feb 13

Fernández-Ruiz J.
Departamento de Bioquímica y Biología Molecular and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Facultad de Medicina, Universidad Complutense, Madrid, Spain.
AbstractThere is evidence that cannabinoid-based medicines that are selective for different targets in the cannabinoid signalling system (e.g. receptors, inactivation mechanism, enzymes) might be beneficial in basal ganglia disorders, namely Parkinson's disease (PD) and Huntington's disease (HD).
These benefits not only include the alleviation of specific motor symptoms [e.g. choreic movements with cannabinoid receptor type 1 (CB(1))/transient receptor potential vanilloid type 1 agonists in HD; bradykinesia with CB(1) antagonists and tremor with CB(1) agonists in PD], but also the delay of disease progression due to the neuroprotective properties demonstrated for cannabinoids (e.g. CB(1) agonists reduce excitotoxicity; CB(2) agonists limit the toxicity of reactive microglia; and antioxidant cannabinoids attenuate oxidative damage).
In addition, extensive biochemical, anatomical, physiological and pharmacological studies have demonstrated that:
(i) the different elements of the cannabinoid system are abundant in basal ganglia structures and they are affected by these disorders;
(ii) the cannabinoid system plays a prominent role in basal ganglia function by modulating the neurotransmitters that operate in the basal ganglia circuits, both in healthy and pathological conditions;
and (iii) the activation and/or inhibition of the cannabinoid system is associated with important motor responses that are maintained and even enhanced in conditions of malfunctioning and/or degeneration.
In this article we will review the available data regarding the relationship between the cannabinoid system and basal ganglia activity, both in healthy and pathological conditions and will also try to identify future lines of research expected to increase current knowledge about the potential therapeutic benefits of targeting this system in PD, HD and other basal ganglia disorders.
PMID: 19220290 [PubMed - indexed for MEDLINE]PMCID: PMC2697699Free PMC Article

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