Huntington's Disease

Excerpt from www.alzheimer.ca:

Huntington's disease is an inherited disease that causes certain nerve cells in the brain to waste away. People are born with the defective gene, but symptoms usually don't appear until middle age.

HD is a familial disease, passed from parent to child through a mutation in the normal gene. Anyone with a parent with Huntington's has a 50 percent chance of inheriting the gene, and everyone who inherits it will eventually develop the disorder. In about 1 to 3 percent of cases, no history of the disease can be found in other family members.

Recent Pat CNS Drug Discov. 2012 Apr 1;7(1):41-8.

Cannabinoids: novel medicines for the treatment of Huntington's disease.

Sagredo O, Pazos MR, Valdeolivas S, Fernandez-Ruiz J.

Source

Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Universidad Complutense, 28040-Madrid, Spain. onintza@med.ucm.es

Abstract

Cannabinoid pharmacology has experienced a notable increase in the last 3 decades which is allowing the development of novel cannabinoid-based medicines for the treatment of different human pathologies, for example, Cesamet® (nabilone) or Marinol® (synthetic Δ9-tetrahydrocannabinol for oral administration) that were approved in 80s for the treatment of nausea and vomiting associated with chemotherapy treatment in cancer patients and in 90s for anorexiacachexia associated with AIDS therapy. Recently, the british company GW Pharmaceuticals plc has developed an oromucosal spray called Sativex®, which is constituted by an equimolecular combination of Δ9-tetrahydrocannabinol- and cannabidiol- enriched botanical extracts. Sativex® has been approved for the treatment of specific symptoms (i.e. spasticity and pain) of multiple sclerosis patients in various countries (i.e. Canada, UK, Spain, New Zealand). However, this cannabis- based medicine has been also proposed to be useful in other neurological disorders given the analgesic, antitumoral, anti-inflammatory, and neuroprotective properties of their components demonstrated in preclinical models. Numerous clinical trials are presently being conducted to confirm this potential in patients. We are particularly interested in the case of Huntington's disease (HD), an autosomal-dominant inherited disorder caused by an excess of CAG repeats in the genomic allele resulting in a polyQ expansion in the encoded protein called huntingtin, and that affects primarily striatal and cortical neurons thus producing motor abnormalities (i.e. chorea) and dementia. Cannabinoids have been studied for alleviation of hyperkinetic symptoms, given their inhibitory effects on movement, and, in particular, as disease-modifying agents due to their anti-inflammatory, neuroprotective and neuroregenerative properties. This potential has been corroborated in different experimental models of HD and using different types of cannabinoid agonists, including the phytocannabinoids present in Sativex®, and we are close to initiate a clinical trial with this cannabis-based medicine to evaluate its capability as a disease-modifying agent in a population of HD patients. The present review will address all preclinical evidence supporting the potential of Sativex® for the treatment of disease progression in HD patients. The article presents some promising patents on the cannabinoids.

PMID:
22280340
[PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/22280340

Microglial CB_2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity

. Javier Palazuelos[1,2], Tania Aguado[1,2], M. Ruth Pazos[1,3], Boris Julien[1,2], Carolina Carrasco[1,2], Eva Resel[1,2], Onintza Sagredo[1,3], Cristina Benito[1,4], Julián Romero[1,4], Iñigo Azcoitia[5], Javier Fernández-Ruiz[1,3], Manuel Guzmán[1,2] and Ismael Galve-Roperh[1,2]

+

Received March 27, 2009.
Revision received July 28, 2009.
Accepted August 3, 2009.

Summary

Cannabinoid-derived drugs are promising agents for the development of novel neuroprotective strategies. Activation of neuronal CB_1 cannabinoid receptors attenuates excitotoxic glutamatergic neurotransmission, triggers prosurvival signalling pathways and palliates motor symptoms in animal models of neurodegenerative disorders. However, in Huntington's disease there is a very early downregulation of CB_1 receptors in striatal neurons that, together with the undesirable psychoactive effects triggered by CB_1 receptor activation, foster the search for alternative pharmacological treatments. Here, we show that CB_2 cannabinoid receptor expression increases in striatal microglia of Huntington's disease transgenic mouse models and patients. Genetic ablation of CB_2 receptors in R6/2 mice, that express human mutant huntingtin exon 1, enhanced microglial activation, aggravated disease symptomatology and reduced mice lifespan. Likewise, induction of striatal excitotoxicity in CB_2 receptor-deficient mice by quinolinic acid administration exacerbated brain oedema, microglial activation, proinflammatory-mediator state and medium-sized spiny neuron degeneration. Moreover, administration of CB_2 receptor-selective agonists to wild-type mice subjected to excitotoxicity reduced neuroinflammation, brain oedema, striatal neuronal loss and motor symptoms. Studies on ganciclovir-induced depletion of astroglial proliferation in transgenic mice expressing thymidine kinase under the control of the glial fibrillary acidic protein promoter excluded the participation of proliferating astroglia in CB_2 receptor-mediated actions. These findings support a pivotal role for CB_2 receptors in attenuating microglial activation and preventing neurodegeneration that may pave the way to new therapeutic strategies for neuroprotection in Huntington's disease as well as in other neurodegenerative disorders with a significant excitotoxic component.

Loss of striatal type 1 cannabinoid receptors is a key pathogenic factor in Huntington's disease

. Cristina Blázquez[1,2], Anna Chiarlone[1,2], Onintza Sagredo[1,3], Tania Aguado[1,2], M. Ruth Pazos[1,3], Eva Resel[1,2], Javier Palazuelos[1,2], Boris Julien[1,2], María Salazar[1,2], Christine Börner[4], Cristina Benito[1,5], Carolina Carrasco[1,2], María Diez-Zaera[1,6], Paola Paoletti[1,7], Miguel Díaz-Hernández[1,8], Carolina Ruiz[1,9], Michael Sendtner[10], José J. Lucas[1,8], Justo G. de Yébenes[1,9], Giovanni Marsicano[11], Krisztina Monory[12], Beat Lutz[12], Julián Romero[1,5], Jordi Alberch[1,7], Silvia Ginés[1,7], Jürgen Kraus[4], Javier Fernández-Ruiz[1,3], Ismael Galve-Roperh[1,2] and Manuel Guzmán[1,2]
+

Received April 8, 2010.
Revision received June 11, 2010.
Accepted August 2, 2010.

Summary

Endocannabinoids act as neuromodulatory and neuroprotective cues by engaging type 1 cannabinoid receptors. These receptors are highly abundant in the basal ganglia and play a pivotal role in the control of motor behaviour. An early downregulation of type 1 cannabinoid receptors has been documented in the basal ganglia of patients with Huntington's disease and animal models. However, the pathophysiological impact of this loss of receptors in Huntington's disease is as yet unknown. Here, we generated a double-mutant mouse model that expresses human mutant huntingtin exon 1 in a type 1 cannabinoid receptor-null background, and found that receptor deletion aggravates the symptoms, neuropathology and molecular pathology of the disease. Moreover, pharmacological administration of the cannabinoid Δ^9-tetrahydrocannabinol to mice expressing human mutant huntingtin exon 1 exerted a therapeutic effect and ameliorated those parameters. Experiments conducted in striatal cells show that the mutant huntingtin-dependent downregulation of the receptors involves the control of the type 1 cannabinoid receptor gene promoter by repressor element 1 silencing transcription factor and sensitizes cells to excitotoxic damage. We also provide in vitro and in vivo evidence that supports type 1 cannabinoid receptor control of striatal brain-derived neurotrophic factor expression and the decrease in brain-derived neurotrophic factor levels concomitant with type 1 cannabinoid receptor loss, which may contribute significantly to striatal damage in Huntington's disease. Altogether, these results support the notion that downregulation of type 1 cannabinoid receptors is a key pathogenic event in Huntington's disease, and suggest that activation of these receptors in patients with Huntington's disease may attenuate disease progression.

http://brain.oxfordjournals.org/content/134/1/119.abstract

Neuropharmacology. 2015 Feb;89:368-74. doi: 10.1016/j.neuropharm.2014.07.021. Epub 2014 Aug 11.

Chronic cannabinoid receptor stimulation selectively prevents motor impairments in a mouse model of Huntington's disease.

Pietropaolo S[1], Bellocchio L[2], Ruiz-Calvo A[2], Cabanas M[3], Du Z[3], Guzmán M[2], Garret M[3], Cho YH[3].

Author information

Abstract

Huntington's disease (HD) is a devastating neurodegenerative disease characterized by a progressive decline in motor abilities, as well as in cognitive and social behaviors. Most of these behavioral deficits are recapitulated in the R6/1 transgenic mouse, which can therefore be used as an experimental model to identify the neurobiological substrates of HD pathology and to design novel therapeutic approaches. The endocannabinoid system (ECS) is a relevant candidate to participate in the etiopathology of HD as it is a key modulator of brain function, especially in areas primarily affected by HD dysfunction such as the striatum. Thus, some studies have demonstrated an association between HD progression and alterations in the expression of several ECS elements, thereby suggesting that improving ECS function may constitute a useful strategy to eliminate or at least delay the appearance of HD symptoms. Here this hypothesis was specifically tested by evaluating whether the administration of a well-characterized cannabinoid receptor agonist (WIN 55,212), either acutely or chronically, improves the HD-like symptoms in R6/1 mice. While acute treatment did not change the behavioral phenotype of transgenic animals, chronic administration was able to prevent the appearance of motor deficits, to increase the number of striatal huntingtin inclusions and to prevent the loss of striatal medium-sized spiny neurons, without affecting the social or cognitive alterations. These findings suggest that prolonged administration of cannabinoid receptor agonists could be an appropriate strategy for selectively improving motor symptoms and stimulating neuroprotective processes in HD patients.

PMID:
25123645
[PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/25123645

Neuroscience. 2009 Sep 29;163(1):456-65. doi: 10.1016/j.neuroscience.2009.06.014. Epub 2009 Jun 10.

Altered CB1 receptor and endocannabinoid levels precede motor symptom onset in a transgenic mouse model of Huntington's disease.

Dowie MJ[1], Bradshaw HB, Howard ML, Nicholson LF, Faull RL, Hannan AJ, Glass M.

Author information

Abstract

Huntington's disease (HD) is an inherited neurodegenerative disease characterised by cell dysfunction and death in the basal ganglia and cortex. Currently there are no effective pharmacological treatments available. Loss of cannabinoid CB1 receptor ligand binding in key brain regions is detected early in HD in human postmortem tissue [Glass M, Dragunow M, Faull RL (2000) The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 97:505-519]. In HD transgenic mice environmental enrichment upregulates the CB1 receptors and slows disease progression [Glass M, van Dellen A, Blakemore C, Hannan AJ, Faull RL (2004) Delayed onset of Huntington's disease in mice in an enriched environment correlates with delayed loss of cannabinoid CB1 receptors. Neuroscience 123:207-212]. These findings, combined with data from lesion studies have led to the suggestion that activation of cannabinoid receptors may be protective. However, studies suggest that CB1 mRNA may be decreased early in the disease progression in HD mice, making this a poor drug target. We have therefore performed a detailed analysis of CB1 receptor ligand binding, protein, gene expression and levels of endocannabinoids just prior to motor symptom onset (12 weeks of age) in R6/1 transgenic mice. We demonstrate that R6/1 mice exhibit a 27% decrease in CB1 mRNA in the striatum compared to wild type (WT). Total protein levels, determined by immunohistochemistry, are not significantly different to WT in the striatum or globus pallidus, but are significantly decreased by 19% in the substantia nigra. CB1 receptor ligand binding demonstrates significant but small decreases (<20%) in all basal ganglia regions evaluated. The levels of the endocannabinoid 2-arachidonoyl glycerol are significantly increased in the cortex (147%) while anandamide is significantly decreased in the hippocampus to 67% of WT. Decreases are also apparent in the ligand binding of neuronal D1 and D2 dopamine receptors co-located with CB1, while there is no change in GABA(A) receptor ligand binding. These results suggest that in this R6/1 mouse colony at 12 weeks there are only very small changes in CB1 protein and receptors and thus this would be an appropriate time point to evaluate therapeutic interventions.

PMID:
19524019
[PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/19524019