

Are cannabinoid receptor knockout mice animal models for schizophrenia?

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Summary Schizophrenia is a devastating psychiatric disorder with a high prevalence worldwide. There is therefore a need for animal models allowing the development of new therapeutic interventions and reliable diagnostic tests. In the temporal domain, cannabinoid receptor gene (CB1) knockout mice exhibit behavioural alterations, which parallel symptoms in schizophrenia, cannabis intoxication and dopamine D2 activation. While a specific nucleotide homology between CB1 and D2 accounts for the pathophysiology, pre-inserted spirochaetal DNA on the polyadenylation signal of CB1 reveals the aetiology of schizophrenia. If, in analogy to thalassaemia, mutations occur within this 3' regulatory domain, the genetic expression of CB1 is disrupted and sequential information lost in time. CB1, previously unrecognized as a candidate gene, thus unifies the different aspects of schizophrenic psychosis: cannabis-induced model psychosis, disrupted information processing, spatio-temporal distortions and other psychotic symptoms, disturbed neuronal migration, schizophrenic brain disorder, familial transmission, and prenatal infection by *Borrelia burgdorferi*. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Schizophrenia – a break between reality, mind, and emotion – is a psychiatric disorder characterized by symptoms such as hallucinations, delusions, reduced motivation, and deterioration of social functioning. Apart from its devastating impact on individuals and their families, its prevalence of at least 1% worldwide creates a huge economic burden for society. Although a genetic background is widely accepted, the pathogenesis of schizophrenia remains obscure, so far. There is therefore a need for an animal model allowing the development of new therapeutic interventions and diagnostic tests.

Despite increasing numbers of reported candidate regions for schizophrenia, no major mutations cosegregating with schizophrenia have been detected in candidate genes. This poses a considerable challenge to

the genetic psychiatrist. Unfortunately, CB1 knockout mice do not talk about their hallucinations to the psychiatrist, and the geneticist does not understand the language of schizophrenics.

CB1, TIME AND SPEECH

Because of reduced sequential information-processing, schizophrenic speech appears to be stereotyped (1) and, in cannabis-induced psychosis, as well as in schizophrenia, temporal distortions have been reported with considerable consistency (2,3).

In our central nervous system or any other dynamical system of three and higher dimensions, the flow of information is continuously converging and being lost while generating information in another dimension. The temporal information thus gained is defined as sequential information, or Kolmogorov entropy (4), which increases at the end and initiation of each goal-directed motor activity (5). In addition, P300 event-related potentials correlate with attention across time (6) and sequential perception of preceding signals and subsequent goal-directed action (7).

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P300 event-related potentials, which are among the most robust indices for schizophrenia (8), constitute electroencephalographic indices for cannabis intoxication (9) and a genetic polymorphism of the CB1 receptor (10). Its pharmacological agonist delta-9-tetrahydrocannabinol (THC), as well as schizophrenia have been related to temporal illusions – particularly an apparent halt of physical time (2,3,11). Intriguingly, CB1 knock-out mice show reduced initiation of goal-directed behaviour (12) and schizophrenics an additional, sequential reduction of speech (1). A genetic knockout of CB1, which reaches its highest levels in areas known to represent time (6) and language (13), could thus account for the disruption of temporal representations in mice and speech – the highest form of sequential behaviour in man.

CB1 AND D2: GENETIC CORRELATE

In humans, the function of the dopamine D2 receptor, which is an important pharmacological target for the treatment of schizophrenia, can be correlated with an apparent halt of physical time (11), as well. Like CB1 (10) a genetic polymorphism of D2 also shows alterations of the P300 event-related potential (14). However, only CB1, but not D2, lies on a candidate region for schizophrenia (15,16). CB1 is thus predicted to be the candidate gene. The genetic information of CB1 being similar to D2 in its consequences will be necessary for understanding its pathophysiological role in schizophrenia (see Table 1). The additional information resulting from observations of a genetic knock-out of CB1 will be sufficient for its aetiology (see Table 2).

The respective sequences can be found at Online Mendelian Inheritance of Man (15). This comprehensive, authoritative data bank including training programs is easily accessible and very much recommended to anybody interested in applied medical genetics.

Table 1 HOMOLOGIES between CB1 and D1 versus CB1 and D2 encoding the inhibitory 7th trans-membrane loop. In contrast to a silent point mutation from gtg = valine to gtc = valine on D2 of the rat, and atc = isoleucine or att = isoleucine on human D2 and D1, respectively, an effective point mutation occurred within the dopamine D2 receptor gene. This has led to an amino-acid substitution of either gtg = valine on human D2, or alternatively, of ttg = leucine on human D1. As a result, the transcribed amino-acids of this seventh trans-membrane section on CB1 are identical with D2 but dissimilar with D1. This explains the common inhibitory dysfunctions of CB1 and D2.

HOMOLOGIES between CB1 and D1 at the PROTEIN level
Score = 71.0 bits (171), Expect = 2e-11, Identities = 75/320 (23%)
Positives = 137/320 (42%), Gaps = 50/320 (15%).

HOMOLOGIES between CB1 and D2 at the DNA level
Score = 37.2 bits (19), Identities = 19/19 (100%).
CB1 (human) (1172) ccgtgaaccccatcatcta (1187)3' U73304
D2 (human) (1274) ccgtgaaccccatcatcta (1292)3' AF176812
D2 (rat) (1608) ccgtcaaccccatcatcta (1626)3' NM_012547
D1 (human) (974) ccttgaaccccatcattta (992)3' X58987

CB1 shows significant homology with the dopamine D1 – a type I G-protein coupled receptor – at the amino-acid level. However, owing to one specific sequence of 19 homologous base pairs at the nucleotide level, it is the dopamine 2 receptor (D2) – a type II G-protein coupled receptor – which shows significant DNA homology to CB1 (see Table 1). Apart from a silent point mutation from g t g to g t c in the rat D2 receptor gene (*Rattus norvegicus*), which has occurred after the phylogenetic rat mouse divergence 35 million years ago, the homologous nucleotide sequence can be found in all sequenced primate (*H.sapiens*, *Macaca mulatta*, *Cercopithecus aethiops*) and rodent (*Mus musculus*) D2 receptor genes (15). Otherwise, CB1 and D2 are dissimilar.

CB1 AND SCHIZOPHRENIA: PHENOTYPIC CORRELATE

The circumscribed nucleotide homology between the CB1 and the D2 receptors encodes the seventh trans-membrane loop, which is known for the inhibitory-mode (i-mode) of metabotropic action. A prenatal event, interfering with neuronal migration from inner to outer cortical laminae in mid pregnancy, most likely underlies the consistent pattern of cellular disarray observed in schizophrenic brains (17). If the expression of higher levels of CB1 within outer cortical compared to inter-cortical layers (13) results from a CB1 mediated migration of neurons, the inter-cortical disarray might be explained by a knock-out or impaired function of CB1, whose metabotropic i-mode has recently been reported to be crucial for cellular migration (18). The anatomical distribution of CB1 receptors (13) furthermore mirrors the macro-anatomic regions involved in schizophrenia (19) and the regions involved in the conscious processing of time (6). Not surprisingly, high levels of CB1 can also be found in the subiculum, whose myelinating fronto-hippocampal connections may trigger schizophrenia in adolescence (20). And before adolescence, which coincides with the onset of schizophrenia, or dementia praecox as described by Kraepelin (21), a conscious perception of time appears to be immature or non-existent (22).

Correlation of time and space in humans

To bring our experiences into a logical system, science must confine itself to the description of correlations between observable quantities (23). It seems strange that Einstein, realizing the importance of subjective time, relegated this important question to Piaget (22). The greatest outstanding riddle concerns the mismatch between physical and subjective time (23), and how that relates to the sense of free will (24), or in other words, to the freedom of choice – a term that defines information (25).

Table 2 GENETIC KNOCKOUT of human 3' poly-A signal AATAAA by dissimilar DNA of intracellular micro-organisms. Base pairs originating from microbial nucleotides are indicated in upper case, and non-microbial nucleotides in lower case letters. The polyadenylation signals, whose non-redundant code protects foreign DNA from mutations, as well as 3' polyadenylation sites, present safe havens for insertions of microbial virulence factors. In the case of recombination between dissimilar strands (i.e. between **AATAAA** and **AATATA** or **ATAAT**) mismatch repair mutations (\uparrow) may, in analogy to a genetic knock out of β globin in β thalassaemia, result in a knock out of CB1 in schizophrenia.

MICROBIAL VIRULENCE FACTOR within β globin		Poly-A cleavage site
<i>R. prowazekii</i> (232700)	AATAAAAAACATTTAT (232685)5'	↓
human β globin (1711)	AATAAAAAACATTTATt t t c a t t g c a (1736)3'	
Putative knockout by:		
<i>P. falciparum</i>	(470)ATAAGAAACATTTATTT (486)3'	↑
MICROBIAL VIRULENCE CLUSTER within CB1		
(8219) AGTTACCTGGACTCAAATAAAA(8240)3'	<i>C. muridarum</i>	
<i>P. falciparum</i> (<i>rap</i>)	(263)TCAAATAAAAGTTCTA(280)3'	
<i>B. burgd.</i> (<i>p115</i>)	(4133)GATTCAAATAAAAATTCTAAATTACCAT (4160)3'	CB1 Poly-A cleavage site
human CB1	(5493)GAATCAAATAAAAATTCTAGATTACCATGAA g a a c a t a (5530)3'	↓
	(4662) TCTAGATTACCATGAA(4677)3' <i>S. aureus</i>	
Putative knockout by:		
<i>B. burgdorferi</i> (<i>1p28-1</i>)	(7553)AATATAAATTCTATAT (7568)3'	
<i>B. burgdorferi</i> (<i>ospA</i>)	(41)ATAATAATTCTAAATTA(25)5'	

Microbial virulence factors within β globin: *Rickettsia prowazekii*: proline-betaine transporter for the reduction of osmotic stress; *Plasmodium falciparum* in thalassaemia β globin: RNA polymerase III.

Microbial virulence factors within CB1: *Chlamydia muridarum* in CB1: iron binding protein to overcome protective barriers of low iron levels; *Plasmodium falciparum* (*rap*): rhoptry associated protein to penetrate erythrocytes; *Borrelia burgdorferi* (*p115*): related to human chromosome associated protein, binding actin for DNA and probably intracellular locomotion; *Staphylococcus aureus* in CB1: penicillin binding protein; *Borrelia burgdorferi* (*1p28-1*): pseudogene on linear plasmid; *Borrelia burgdorferi* (*ospA*): outer surface protein A, antigen of genetically induced variability.

Despite the immense capacity of our brain there are fewer independent variables than one might expect. When, in cannabis-induced psychosis or schizophrenia (2,3), sequential representations of time (Kolmogorov entropy) decrease, the information concerning the other variable (Shannon entropy) will increase. Otherwise Maxwell's Demon would get us into trouble (26). Instead, Shannon information (defined in spatial terms as a probability distribution over a set of dimensions) will provoke a surplus: a pathologic overlap of spatial dimensions and 'inner-outer' confusion. Schizophrenic patients with delusions of alien control have precisely this problem, as shown by concomitant shifts of over-activation to the right hemispheric cingular gyrus, where 'inner' and 'outer' space is normally represented (27).

The distorting effect of THC on the representation of time and space corroborates the long-held hypothesis that cannabis intoxication might be able to reveal the origin of psychosis (28). That large doses of cannabis are hallucinogenic has been known for thousands of years and is the reason for ritual consumption. The loss of time sense must have induced experiences of 'timelessness' or 'immortality', and the disintegration of the subject-object boundary feelings of ecstasy and mystic union with the 'immortal': the worshippers felt the divinity within and without themselves (29). In contemporary India, the ritual term for cannabis is *amrita*, being etymologically equivalent to ambrosia – the potion of the immortals, the potion of immortality.

Correlation of space and time in mice

At the symptomatic level, the nucleotide homology between and CB1 and the D2 elucidates another puzzling dysfunction CB1 knock-out mice experience. Compared with normal controls, *i*-mode 'disinhibition' of NMDA enhances their spatial long-term memories (hippocampal long-term potentiation) (30,31), while complementary, goal-directed temporal representations are decreased (12). This reflects the complementary relationship between Kolmogorov and Shannon information (26).

The mnemonic effect in mice is consistent with the psychotic symptoms in schizophrenia. Despite the fact that patients with tertiary neurosyphilis do hallucinate, they apparently do not remember (or 'reconnect') their hallucinations as a fixed delusion (21). Hence, the difference between dementia praecox (schizophrenia) and syphilitic dementia is that, without memory, hallucinations are lost, and that the thoughts of schizophrenics are flooded with fixed hallucinations, expanding into overt delusions.

'Disinhibition' and genetic 'background'

Because a pharmacological blockade of the CB1 receptor produces opposite and CB1 agonists similar effects, the phenotypic changes in CB1 knock-out mice are counter-intuitive. The paradoxical behaviour (12,30), however, is consistent with the postulated overlap between schizophrenia and cannabis-induced psychosis. It does not

reflect a direct effect of CB1 receptor dysfunction, but rather appears to be related to the altered gene expression of the genetic background and subsequent neuro-developmental changes in striatal pathways (12).

CB1 disruption may result in 'disinhibition' of neurons, which trigger increases in substance P and dynorphin gene expression. Increased levels of mRNA for dynorphin, especially in those regions that are normally rich in CB1 receptors (12), might account for the differences in acute versus chronic inactivation of the CB1 receptor (30). Intriguingly, the CB1 agonist (THC), and the endogenous cannabinoid, anandamide, are known to enhance dynorphin release (32). In schizophrenia, elevated levels of dynorphin have been reported, as well (33).

CB1 knockout mice appear healthy, are fertile, have normal body-weight, and do not exhibit any obvious morphological abnormalities. But, over time, the mice die suddenly without any obvious signs of disease, and pathological examination does not reveal any obvious cause of death. Although the reason for this significantly increased mortality is currently unknown, CB1 knockout mice may have an increased risk of developing neurological problems such as seizures – another possible manifestation of CB1 disinhibition (34). This further substantiates the view of an epileptic dysfunction in schizophrenic psychosis (2), a correlation that has intrigued clinical observers since before the turn of the century.

CB1 AND SCHIZOPHRENIA: AETIOLOGICAL CORRELATE

Genetic epidemiology provided consistent evidence over many years that schizophrenia has a complex genetic component, including interaction between many genes (16). It is, however, premature to conclusively reject the idea of one gene of major effect. Multiple insertions of *B. burgdorferi* within the human genome could account for the increasing number of coincident regions reported in schizophrenia. Within the poly A signal (AATAAA) mutations could, in analogy to dysfunctional thalassaemias with mutated poly A signals (35), disrupt the genetic expression of CB1 (see Table 2).

On the 3' regulatory domain of the human CB1 gene, located within a candidate region for schizophrenia at 6q14, a putative virulence factor (p115) originating from *B. burgdorferi* could be identified. Through infectious recombination with another virulence factor of *B. burgdorferi*, the flagellar basal rod protein (fbrp), p115 has introduced the poly-A signal (AATAAA) for the ribosomal the genetic expression of CB1 before the phylogenetic rodent-primate divergence 75 million years ago (see Figs 1 & 2). This sequence, which originally encoded the

flagellar basal rod protein (fbrp), another virulence factor of *B. burgdorferi*, can still be found on the 5' regulatory domain of 5HT1E of mice and rats (15). Overlapping with the CB1 poly-A signal of humans and rats, other insertions of *C. muridarum* nucleotides have occurred, as well (see Table 2). This emphasises the attraction the 3' regulatory domain of CB1 and its poly-A signal exerts on specific microbial DNA to recombine.

That lateral gene transfer has influenced the evolution of eukaryotes is counter-current to established views. However, *B. burgdorferi*, which as an intracellular parasite appears to be excluded from the benefits of lateral gene transfer of virulence factors between micro-organisms (36), has a direct access to host genes. With only an incomplete genome at its disposal, the spirochaete exploits this accessible genetic machinery like a virus for its own replication (37). Only a few other intracellular micro-organisms (see Table 2) express nucleotide sequences, which are homologous to those of their host and thereby not viewed as foreign (38).

Resulting from the process of genomic decay in plasmids, or alternatively, from genetically induced variability of outer surface proteins osp A, dissimilarity between *B. burgdorferi* and its pre-inserted human templates may nevertheless occur. In the case of infectious recombination this may trigger mismatch repair mutations within the poly-A signal and a genetic knock-out of CB1 (see Table 2).

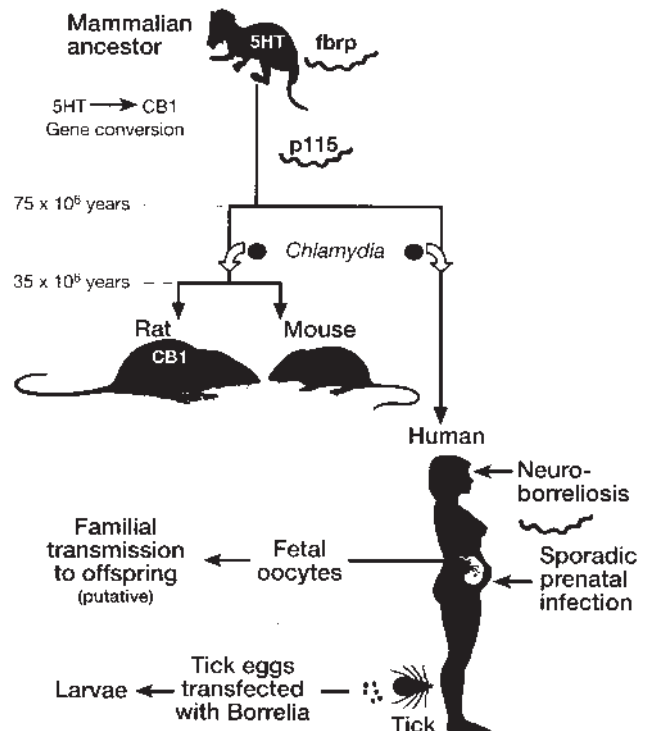


Fig. 1 Genetic integration of *B. burgdorferi* into CB1.

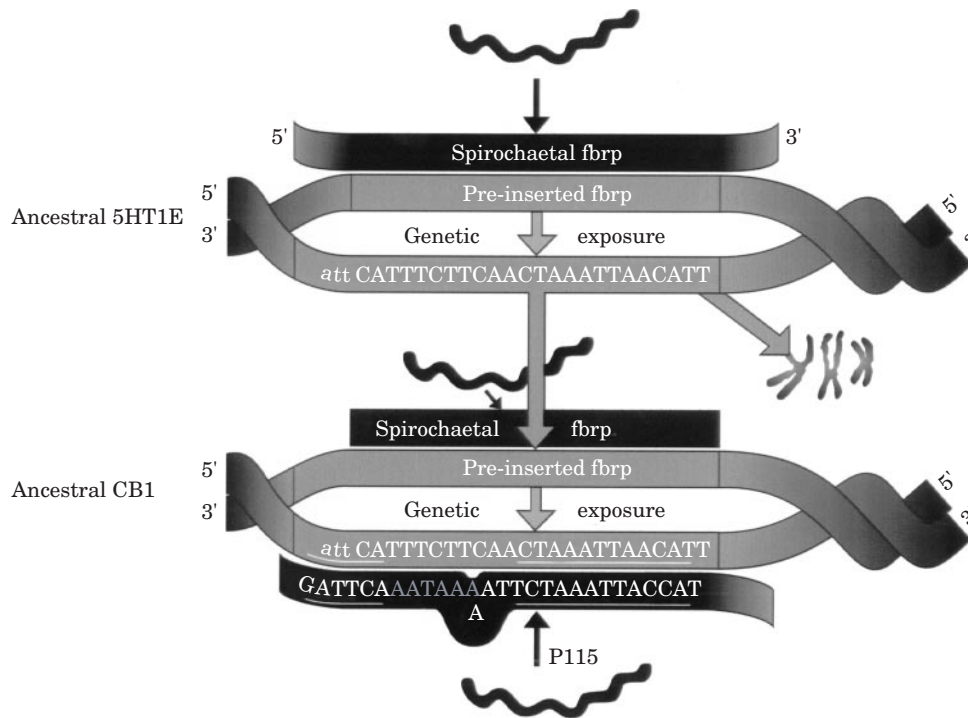


Fig. 2 TRANSLOCATIONS and GENE CONVERSION from ancestral 5HT1E onto CB1. Multiple recombinations between the spirochaetal *fbrp* and its pre-inserted *fbrp* templates have exposed (↓) the complementary strand on the double helix, including adjacent non-microbial nucleotides, to further recombination with both microbial and ancestral DNA. From ancient 5HT1E harbouring *B. burgdorferi*, a gene conversion occurred from 5HT1E to CB1, which are both located adjacent to each other on the 6q14 candidate region for schizophrenia, in addition to numerous translocations all over the human genome. Since the first three nucleotides (att) can still be found on 5HT1E of the mouse (*Mus musculus*) and rat (*Rattus norvegicus*), but not on *fbrp* of *Borrelia burgdorferi*, the spirochaetal template on the CB1 gene originates from ancient 5HT1E already containing the spirochaetal inclusion, and not from a direct transposition of *B. burgdorferi* onto 6q14. Observe the 'loop-hole', inserting an additional nucleotide into CB1. Homologous recombination and mismatch-repair mutation between *B. burgdorferi* p115 and the borrelia template *fbrp* has thus introduced the polyadenylation signal **AATAAA**, which encodes the ribosomal translation and actual genetic expression of CB1.

PREDICTION

The phylogenetic trace within the human genome implies that lateral gene transfer and infectious recombination with *B. burgdorferi* has occurred, and that novel mutations within pre-inserted spirochaetal templates on CB1 are likely to reoccur. If fetal infection by *B. burgdorferi* in early pregnancy coincides with the summer season of tick-borne borreliosis, we would expect a worldwide excess of winter births, as well as a geographical overlap of its vector, the *Ixoid*-tick, with areas of increased risk for sporadic schizophrenia. This is indeed the case (39).

If, in analogy to neurotropic murine leukemia virus infections (40), *B. burgdorferi* infects and mutates oligocellular blastulas in early pregnancy, we would expect a transfection of germ line cells leading to familial transmission of the disease. In humans, sporadic prenatal infection by *B. burgdorferi* has been documented, and in ticks infected by *B. burgdorferi* transfection of oocytes occurs, as well (41) (see Fig. 1).

Like adult neuroborreliosis, which can also produce symptoms indistinguishable from schizophrenia (42),

sporadic schizophrenia is characterized by an excess of focal neurological damage (43). Sporadic infection restricted to the fetal brain will thus result in a brain disorder, whose severity depends on the proportion of neurons involved. If recombination between *B. burgdorferi* and its pre-inserted templates occurs also in the germ line, initiating familial schizophrenia from a sporadic case (see Fig. 1), mismatch-repair mutations will encompass all neurons in the offspring. The phenotypic onset of disordered integrative functions (43) is then expected to be more severe and earlier (so called anticipation, see 15).

The present hypothesis of *B. burgdorferi* as the major causative factor for schizophrenia is to be falsified, if it can be shown by genetic analysis of the CB1 polyadenylation site, post mortem autoradiographic studies (13), or in vivo radioligand binding (44) that the majority of schizophrenics do express a physiological amount of functional CB1 receptors – in the familial cases in part, or in the sporadic cases all over the central nervous system.

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