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Letter to the Editor

Lateral Gene Transfer of Foreign DNA:
The Missing Link Between Cannabis Psychosis and Schizophrenia

To The Editor:

The latest intriguing news on *Schizophrenia and the Cannabinoid Receptor Type 1* (*CB1*) by Leroy et al. [2001] corroborates Moreau de Tour's long held hypothesis [1845] that cannabis and its pathophysiological effects [Fritzsche, 2002] lie at the root of this psychiatric disorder. But how can they account for the mutation (G-A) on CB1 being less frequent in cannabis abusing schizophrenic patients, compared to non-substance abusing patients? Does the silent point mutation—which has in fact no functional consequence for CB1 at the protein level—play an unexpected, protective role at the genetic level? Or does the polymorphism point to a schizophrenic risk factor other than cannabis abuse in terms of genetic instability? According to the authors [Leroy et al., 2001] "this marker could be associated with a nearby functional variation of the gene, which remains to be found"—an important conclusion that deserves further comments (Fig. 1).

Cannabinoid transmission is closely related to dopaminergic transmission, but the function of CB1 is not limited to the inhibitory mode of G protein coupled action, as mentioned by Leroy et al. [2001]. Depending on a mutual co-activation between CB1 and dopamine D2, receptor transduction hinges, rather, on the physiological balance between the inhibitory (G-i) and the stimulatory (G-s) mode of CB1 metabotropic action [Glass and Felder, 1997] (Fig. 2).

Cannabinoid receptors can be found all over the basal ganglia, although some preference may exist for the GABAergic direct pathway expressing dopamine D1, substance P, and dynorphin A—an area to which structural schizophrenic changes typically localize. One important neurophysiological constraint of the striatal GABAergic neurons is their bistable membrane potential, allowing for either a constrictive down-state or a potentiated up-state at the dynamic ensemble. A switch to the up-state could thus be induced by coincident CB1-D2 activity, known to augment the concentration of cAMP through G-s [Glass and Felder, 1997]. This dual mode of cannabinoid transmission is reflected at the genetic and phenotypic level in the context of schizophrenic pathophysiology (see Fig. 2).

It is well known that dopaminergic psychostimulants produce paranoid delusions indistinguishable from schizophrenia. As molecular chemistry became more sophisticated, the interaction of drugs with multiple receptor subtypes indeed pointed to similar dopaminergic binding pockets in different G-protein coupled receptors. What was not appreciated until recently [Fritzsche, 2001] was the different genetic relatedness between CB1 and the dopamine D1 and D2 receptors, respectively. While a short sequence of the seventh transmembrane loop being essential for (Gi) transduction shares DNA and protein homology between CB1 and the dopamine D2 receptor (characterized as a type II G-i protein coupled receptor), a much large portion of the CB1 peptide is similar to D1 (being a type I G-s protein coupled receptor).

Cannabis intoxication (through CB1 receptor activation), as well as schizophrenia, exhibits phenotypic changes in the neurotransmitter profile that are surprisingly similar to CB1 receptor knockout mice [Fritzsche, 2001]. This paradoxical effect cannot be derived directly from a putative CB1 receptor dysfunction. In analogy to prefrontal D1 activation [Goldman-Rakic et al., 2000], it appears, rather, to be related to a bell-shaped range of CB1-D2 co-activation, whose dysbalance (or loss of presynaptic G-s transduction) elevates dynorphin A in either case (see Fig. 2).

Dynorphin A is a potent hallucinogenic kappa-opiate receptor agonist, known to induce symptoms of depersonalization and loss of self-control, as well as disturbances in the perception of time. When naloxone (Narcan®), a kappa opiate antagonist, was tested in schizophrenic patients, their hallucinations disappeared promptly. After five minutes, one patient reported "complete silence within his head", and two hours after the naloxone injection another patient with paranoid visual hallucinations noted that the phantom "had left her for the first time in several weeks" [Gunne et al., 1977] Rather than the slow therapeutic effects of

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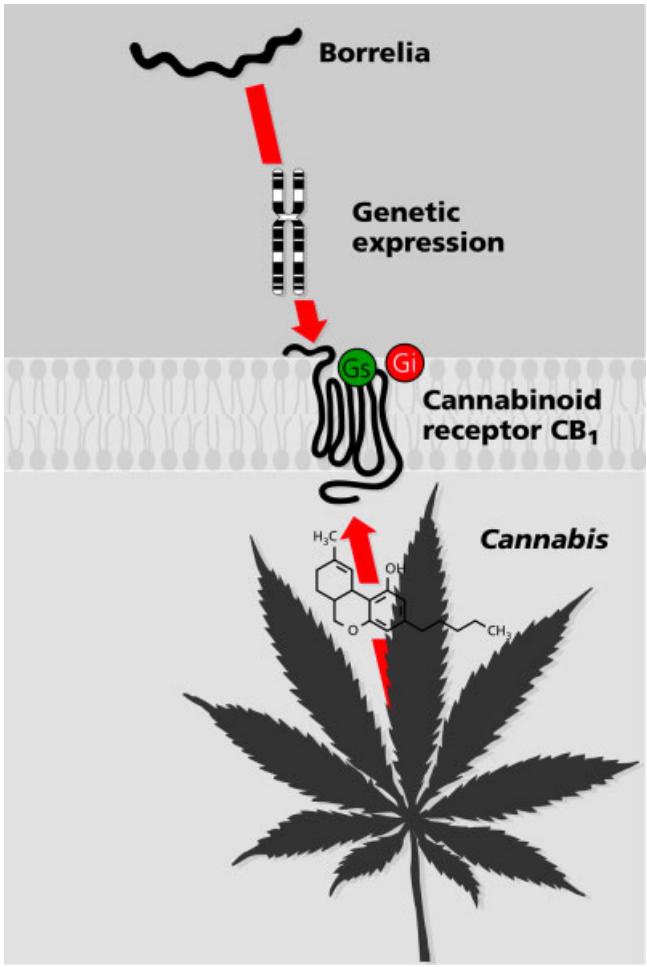

Fig. 1. Cannabis intoxication versus genetic variation of CB1 induced by *Borrelia burgdorferi* DNA. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

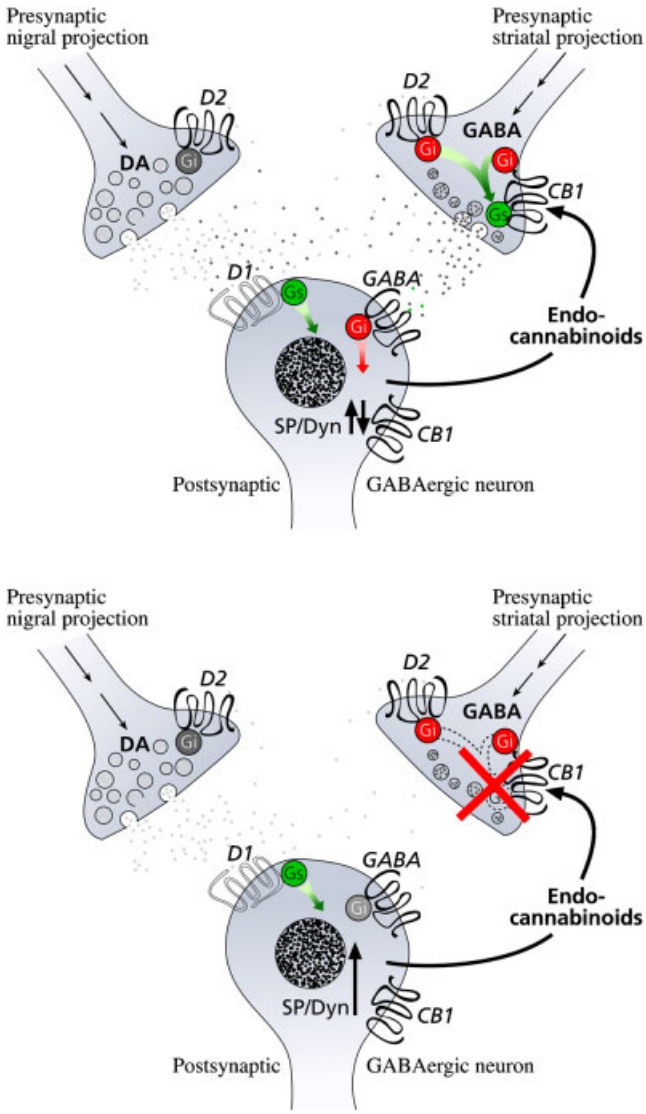

Fig. 2. **Top:** Owing to the functional overlap between the dopamine and the cannabionid systems at the molecular and genetic level, balanced coactivation of both D2 and CB1 stimulates the adenylatecyclase through the 3rd transmembrane G-s protein coupled loop, whereas overactivation of D2 or CB1 through the 7th transmembrane G-i coupled loop exerts an inhibitory effect on the release of GABA into the synaptic cleft. **Bottom:** Dysbalanced D2-CB1 receptor coactivation or genetic expression is supposed to diminish the Gs-protein coupled release of GABA from presynaptic striatal neurons. Reduced activation of the postsynaptic GABA receptor subsequently dysbalances the neuron in favor of the Gs-coupled D1 input which will in turn increase the release of substance P (SP) and dynorphin (Dyn) in CB1 knock-out mice and schizophrenic patients. Hence, by blocking dynorphin activity at the kappa opiate receptor, naloxone can immediately antagonize dynorphin A mediated psychotic effects in at least a subgroup of schizophrenia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

D2 antagonists, such a rapid abolishment of hallucinations indicates a more direct effect on the pathophysiological mechanism in schizophrenia [Terenius, 2000].

To elucidate a putative schizophrenic dysfunction of CB1 [Dean et al., 2001] at the 5′ end, Leroy and colleagues are definitely on the right track, yet in the wrong direction. For it is at the 3′ end where a phylogenetic trace of pre-inserted DNA originating from B. burgdorferi [Fraser et al., 1997] might shed new light on the etiology of schizophrenia [Fritzsche, 2001] (Fig. 3).

In comparison to the adjacent control sequences without microbial insertions, genetic exposure by *B. burgdorferi*has furthermore given rise to a high number of translocations across the human genome whose chromosomal distribution is not entirely random (data in preparation). Chromosome 6 harbors most multiple translocations clustering across 6q14-q24 exactly within the candidate region for schizophrenia on 6q13-q25 [Cao et al., 1997; Martinez et al., 1999; Levinson et al., 2000], in close proximity to their putative original spread from 6q14. One template originating from *B. burgdorferi* nucleotides even coincides with the highest lod score for schizophrenia at 6q21 [Cao et al., 1997]. CB1 is located on the candidate region for schizophrenia on 6q14, which has been correlated to a translocation breakpoint in familial schizophrenia [Holland and Gosden, 1990] and a deletion responsible for neurodevelopmental abnormalities, with enlarged cerebral ventricles and abnormal dermatoglyphics [Kumar et al., 1997].

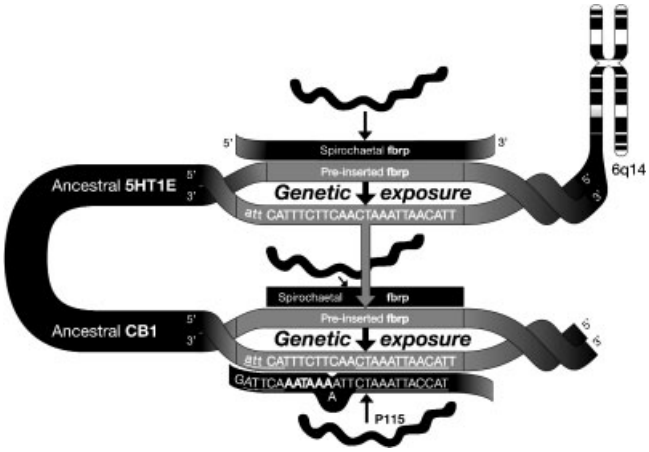

Fig. 3. Infectious recombination between *Borrelia burgdorferi* and human DNA. Within our germline, infectious recombination (↓) between the spirochaetal fbrp and its pre-inserted fbrp template on ancestral 5HT1E exposed (↓) the complementary strand on the double helix, including adjacent non-microbial nucleotides, to further genetic recombination with mammalian and *Borrelia* DNA. Note the apparent gene shuffling from ancestral 5HT1E onto CB1 (⇓). Subsequent recombination with p115 (↑) introduced the polyadenylation signal **AATAAA** into CB1. Since the adjacent non-microbial nucleotides (indicated in lower case letters) can still be found on 5HT1E of the mouse and rat, but not on the fbrp of *Borrelia burgdorferi,*the spread of *B. burgdorferi*DNA originates from the ancient 5HT1E already containing the spirochetal insertion, and not directly from spirochetal nucloeotides (indicated in upper case letters). Adapted from Med Hypotheses [2001] with permission.

Prenatal exposure to foreign DNA, which has led to these multiple germ-line mutations during phylogeny, is likely to reoccur during ontogeny, posing a risk to the unborn of developing schizophrenia later in life. If recombination and mismatch-repair mutations reoccur within the 3′ "hotspot" for pathology [Conne et al., 2000], they will disturb the genetic expression of CB1 in exactly those areas [Glass et al., 1997] that mirror the structural and functional [Silbersweig et al., 1995; Schultz and Andreasen, 1999] brain abnormalities in schizophrenia.

An early prenatal event interfering with neuronal migration [Weinberger, 1995] development of dermatoglyphics [Rosa et al., 2000] and ventricles [Reveley et al., 1982] has been suggested to underlie the consistently reported pattern of cellular disarray in schizophrenic brains [Weinberger, 1995], a hypothesis that contrasts with the frequent reports correlating schizophrenia to third-trimester pregnancy and birth complications due to hypoxic brain damage. The seemingly contradictory findings, however, can be accounted for, as CB1 induces both neuronal migration [Song and Zhong, 2000] and hypoxic resistance to ischemic challenge [Jin et al., 2000].

The spirochetal template P115 identified on CB1, on the other hand, exhibits extensive phylogenetic homology to the human chromosome associated protein hCAP. Being involved in chromosomal replication, accidental recombination between P115 and hCAP at the blastular stage [Silver et al., 1995] might interfere with the replication of a selected number of embryonic cells. In addition to a dysfunctional genetic expression of CB1, we would therefore expect minor chromatin aberrations or non-lethal chromosomal disjunctions of a mosaic distribution to be more likely associated with schizophrenia. This is, in fact, the case. "Conformational changes" of leukocytic chromatin were reported in nine out of ten schizophrenic patients by Issidorides et al. [1975]. The association of the mosaic karyotype of Turner syndrome to schizophrenia, recently reported by Scutt et al. [2001] in this journal is highly significant [Prior et al., 2000; Kawanishi et al., 1997]. Hence, compared to the sequence without mutation, the variation referred to by Leroy et al. [2001] on CB1 (whose underlying template shares a specific nucleotide homology to the *B. burgdorferi* DNA ligase associated virulence factor: AE001157; OMIM: 2002) represents a genetic coincidence that might not be entirely casual.

Cumulative evidence appears to establish that schizophrenic birth excesses are limited to those areas that are endemic for *B. burgdorferi* transmitting ticks and, contrary to current belief, schizophrenia does not occur at a constant, global rate. South of the Wallace Line which limits the spread of *Ixodes* ticks by mammals into New Guinea and Australia [Sonenshine, 1989], seasonal schizophrenic trends are, compared to the Northern Hemisphere, less significant [McGrath and Welham, 1999]. Singapore, which is still a non-endemic area for *Ixodes* ticks [Sonenshine, 1989] and *Borrelia burgdorferi* [Goh et al., 1996], exhibits no schizophrenic birth excess at all [Parker et al., 2000]. In the remote interior of New Guinea, from where neither the presence of *Ixodes* ticks nor Lyme disease [Burkot et al., 1997] has been reported, schizophrenia appears to be non-existent [Dohan et al., 1984, Fritzsche et al., 1990].

The Pacific Coast, New England, and Great Lakes States score an approximately three times higher rate of schizophrenia compared to other states in the USA [Torrey and Bowler, 1990]. Moreover, schizophrenic birth excesses are more pronounced in New England and the Midwest than in the South [Torrey et al., 1977]. This trend, which has been remarkably consistent over a long period, correlates with the geographical distribution of *Ixodes* ticks and Lyme disease [Barbour and Fish, 1993; Brown, 1994; Dennis et al., 1998; Piesman et al., 1999].

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