



Review

Cannabis, psychosis and the thalamus: A theoretical review

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ARTICLE INFO

Article history:

Received 21 August 2012

Received in revised form 21 January 2013

Accepted 19 February 2013

Keywords:

 Δ^9 THC

CBD

T-type calcium channels

Burst firing

Higher order thalamic nuclei

Source-monitoring deficits

ABSTRACT

The role of cannabis in the etiology of schizophrenia has been documented as possibly the strongest environmental risk factor. However, the pathomechanism whereby cannabis use increases this risk has not yet been identified. We argue that this pathomechanism may involve direct effects of exogenous cannabinoids on T-type calcium channels in the thalamus. These channels are crucial for amplification of corticothalamic inputs, as well as for the ability of the thalamus to generate neuronal burst firing. Cortically induced thalamic burst firing has been found to be important in trans-thalamic cortico-cortical interactions. Therefore, any potential interference with the burst firing mode in the thalamus could lead to an impairment in these interactions, which in turn causes a relative disconnection between cortical areas. This in turn could result in reduced ability to recognize re-afferent sensory inputs and psychosis. We also argue that the effects of Δ^9 THC are more detrimental compared with the effects of cannabidiol, as the former may increase the excitability of thalamic neurons by its direct effect on T-type calcium channels.

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1. Introduction

Cannabis sativa, of which marijuana is one derivative, contains a number of ingredients that interact with the endocannabinoid system in the brain (Wilson and Nicoll, 2002). The endogenous ligands for cannabinoid receptors are anandamide and 2-arachidonylglycerol (2-AG), which are synthesized in the neuronal membrane in response to depolarization and act in a retrograde fashion. They are thought to interact with presynaptic cannabinoid receptors and to modulate gamma-aminobutyric

acid (GABA) release from GABA-containing nerve terminals. It has been proposed that the endocannabinoid system serves a neuroprotective function (Marsicano et al., 2003; Pertwee, 2006) among others, and that its disruption by exogenous cannabinoids could lead to neuronal cell loss (Cohen et al., 2008). The use of exogenous cannabis in adolescence has been associated with two- to three-fold increased risk of psychosis (Arseneault et al., 2004; Semple et al., 2005), and it has been argued that the evidence for the role of cannabis in the etiology of schizophrenia is stronger than for any other environmental risk factor (Di Forti et al., 2012; Welch et al., 2011a). However, the pathomechanism whereby cannabis use increases this risk has not yet been identified.

The ratio of the two major cannabinoids found in street cannabis, 9-tetrahydrocannabinol (Δ^9 THC) and cannabidiol (CBD),

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has changed in recent decades. New cannabis strains are reported to have high Δ^9 THC and low CBD composition (Morgan et al., 2010). Recently the results of several studies also suggested that different strains of cannabis have a differential impact on mental health (Bhattacharyya et al., 2009; Di Forti et al., 2009; Morgan et al., 2010). Namely, Δ^9 THC has been proposed to confer the psychosis risk, while there is evidence that CBD does not, and that it even has antipsychotic properties (Zuardi et al., 2006). The cannabis strains that contain a higher proportion of Δ^9 THC compared to CBD have been found to be associated with higher psychosis risk (Morgan and Curran, 2008). Moreover, it was also reported that individuals at genetic risk for psychosis may be more sensitive to both acute (supposedly mood enhancing/anxiolytic/analgesic) and subacute and chronic (probable psychotogenic) effects of cannabis (Henquet and Kuepper, 2010).

In this review, we will discuss the potential implications of non-CB1-receptor mediated effects of the two major constituents of cannabis at the low threshold activated T-type calcium channel sites (Caulfield and Brown, 1992; Ross et al., 2008; Snutch and David, 2006). The T-type calcium channels, encoded by the Ca_v3 genes, activate near resting membrane potentials and generate low-threshold calcium spikes leading to burst firing in some neuronal populations such as in the thalamus (Astori et al., 2011). All three Ca_v3 channel subtypes that encode the pore forming α -subunit of the T-type channels are highly expressed in the thalamocortical system. Based on the analyses of several converging lines of recent experimental and clinical evidence, it is here suggested that exogenous cannabinoids, and in particular Δ^9 THC, confer the increased risk of psychosis by (1) compromising the structural integrity of those thalamic nuclei that are involved in trans-thalamic cortico-cortical interactions, and by (2) interfering with the generation of corticothalamically induced burst firing in the thalamus. These two effects of cannabis in the thalamus in turn worsen trans-thalamic cortico-cortical disconnection, which, as will be argued below and has been argued elsewhere (Guller et al., 2012; Vukadinovic, 2011; Vukadinovic and Rosenzweig, 2012) may be an important aspect of the pathophysiology of schizophrenia. Finally, we also here argue that the previously postulated differential effects of various strains of cannabis, depending on their concentrations of Δ^9 THC and CBD, may be at least partly explained by the dual pharmacodynamics of those two major constituents at the T-type calcium channels in the thalamus.

2. Thalamocortical disconnection in schizophrenia

A number of studies on the involvement of the thalamus in schizophrenia point to a thalamocortical disconnection in this illness. This disconnection, as we will argue in some of the following sections, is potentially worsened by cannabis use, particularly by Δ^9 THC. However, before reviewing these findings, it is important to note some general issues regarding normal thalamic function.

The thalamus and its nuclei have been a focus of several seminal studies by Sherman and Guillery (2006, 2011) who proposed that the thalamus can be subdivided into higher order (HO) and first order (FO) nuclei (Fig. 1A). The HO nuclei such as the mediodorsal (MD) and the pulvinar nuclei receive their main driving inputs from cortical areas and relay these inputs to other cortical areas, while the FO nuclei such as the medial and lateral geniculate nuclei (MGN and LGN) receive their main inputs from the periphery and relay them to their respective primary cortices (in case of MGN and LGN auditory and visual, respectively). It is thought that in contrast to the FO nuclei, the HO nuclei inform wider cortical regions about the ongoing motor instructions. For instance, MD nucleus could serve to inform more posterior cortical areas about ongoing motor commands and planning in the prefrontal cortex

(Fuster, 2008). It was thus proposed that the HO thalamic nuclei are involved in trans-thalamic cortico-cortical communication as well as in the related concept of internal motor monitoring (Sherman and Guillery, 2011).

Importantly, the HO nuclei were also shown to be affected to a greater extent in schizophrenia relative to the FO nuclei (Andrews et al., 2006; Brickman et al., 2004; Byne et al., 2009; Danos et al., 2003) with particular emphasis on the MD and the pulvinar nuclei (Byne et al., 2009). The deficits in HO nuclei have been found to be present early in the course of the illness (Janssen et al., 2012). Moreover, thalamic volume reductions are present in non-affected twins of individuals with schizophrenia, with even greater deficits in affected twins (Ettlinger et al., 2007) suggesting that thalamic volume deficits are associated with increased risk of developing psychosis. The evidence for the involvement of HO nuclei in schizophrenia has potential theoretical significance as it suggests that the illness involves an impairment in trans-thalamic cortico-cortical interactions, which in turn has potential relevance for the proposed failure of internal motor monitoring in psychosis (Vukadinovic, 2011; Vukadinovic and Rosenzweig, 2012). Namely, we propose that the malfunctioning of central internal motor monitoring results in misattribution of self-initiated activity to outside sources and may underlie certain symptoms of schizophrenia (Feinberg, 2011; Frith et al., 2000; Malenka et al., 1986; Vukadinovic, 2011; Vukadinovic and Rosenzweig, 2012). Related to this idea is the finding that the illness is associated with source-monitoring deficits (Anselmetti et al., 2007; Brebion et al., 2000; Ford et al., 2002, 2007; Franck et al., 2001; Johns et al., 2001; Keefe et al., 1999, 2002; Woodward et al., 2008), whereby sensory consequences of self-initiated motor outputs become attributed to outside sources. In particular, this pathomechanism has been found to underlie auditory hallucinations (Kumari et al., 2010). The authors of this study found that impaired speech self-monitoring in schizophrenia is associated with reduced activation of a neuronal network that includes the frontotemporal regions and the thalamus. They concluded that the speech self-monitoring deficits are related to auditory hallucinations, and that they share a common neuronal network dysfunction.

In support of the concept of impaired trans-thalamic cortico-cortical interactions in schizophrenia, Guller et al. (2012) found that in individuals with schizophrenia, transcranial magnetic stimulation (TMS) stimulation of the precentral gyrus resulted in reduced thalamic activation as measured by concurrent functional neuroimaging. Additionally, subsequent secondary cortical activation was also markedly reduced, which was in turn statistically related to the reduced activation in the thalamus. Moreover, the abnormal activation in the thalamus and secondary cortical areas was correlated to the severity of positive symptoms. Thus, there is neuroanatomical (reduction in HO nuclei) as well as experimental support for the concept of impaired trans-thalamic cortico-cortical interactions in schizophrenia, which could in turn have explanatory relevance for the genesis of psychosis and for the psychosis-associated source-monitoring deficits.

3. Brain rhythm abnormalities in schizophrenia

In addition to the structural thalamic abnormalities in schizophrenia that point to impaired trans-thalamic cortico-cortical communication, recent findings regarding brain rhythm abnormalities in sleep and wakefulness are also consistent with this concept.

Firstly, a number of recent studies have found that schizophrenia is associated with a marked reduction in sleep spindles (Ferrarelli et al., 2007, 2010; Seeck-Hirschner et al., 2009; Manóach et al., 2010; Wamsley et al., 2012). Sleep spindles are 11–16 Hz

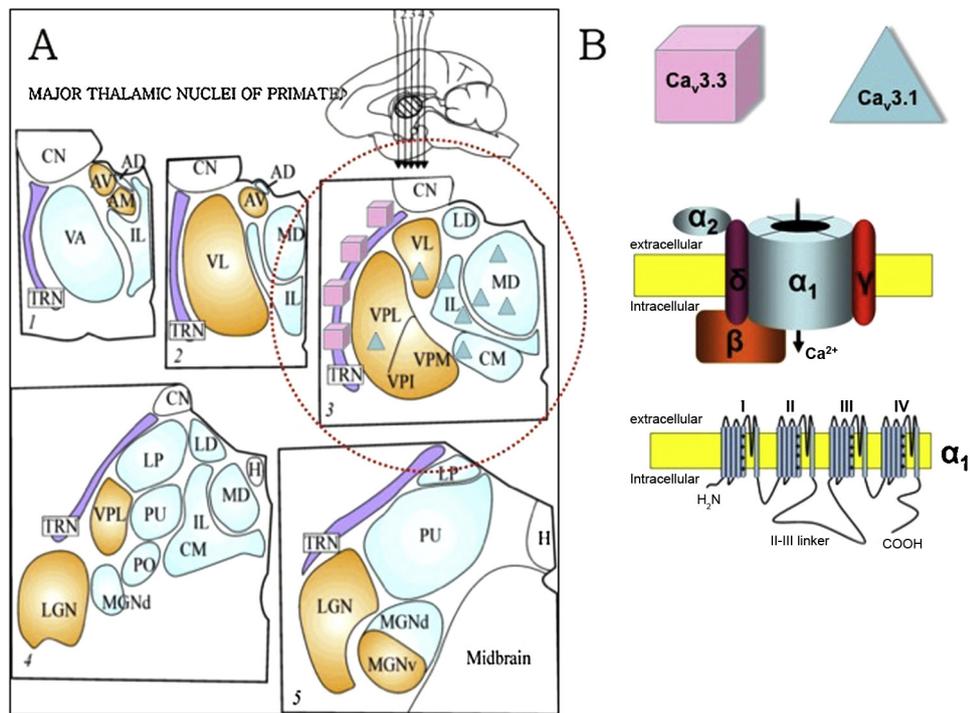


Fig. 1. Schematic view of the major thalamic nuclei in one hemisphere are shown for a generalized primate (A); adopted from Sherman and Guillery (2006) with permission. The sections are numbered 1 through 5 and were cut in the coronal planes indicated by the arrows in the upper right mid-sagittal view. The nuclei filled in yellow are first order nuclei. The regional anatomical variability of Cav3.1 and Cav3.3 T-type calcium channels is suggested on the Section 3, which is circled. The majority of Cav3.3 channels (depicted by the cubes) are found in the TRN, while Cav3.1 channels (depicted by the triangles) are predominantly expressed in the thalamic relay nuclei; for more in depth details please refer to the text (Astori et al., 2011; Talley et al., 1999). In B, the general structure as well as the transmembrane topology of the its α_1 subunit is also shown, adapted from, and as described in Iftinca (2011) where more in detail description can be found. *Abbreviations:* AD, anterodorsal nucleus; AM, anteromedial nucleus; AV, anteroventral nucleus; CM, centromedian nucleus; CN, caudate nucleus; H, habenular nucleus; IL, intralaminar (and midline) nuclei; LD, lateral dorsal nucleus; LGN, lateral geniculate nucleus; LP, lateral posterior nucleus; MD, mediodorsal nucleus; MGN, medial geniculate nucleus; PO, posterior nucleus; PU, pulvinar; TRN, thalamic reticular nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VPI, VPL, VPM, are the inferior, the lateral and the medial parts of the ventral posterior nucleus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

oscillatory bursts of synchronous neuronal firing lasting up to several seconds and involving thalamocortical, corticothalamic and intra-thalamic neuronal interactions (Buzsaki, 1991). Spindles are recorded by electroencephalographic (EEG) recordings and are found in stages 2 and 3 of non-rapid eye movement (NREM) sleep. They are initiated by corticothalamic volleys of action potentials, and subsequently, involve further thalamocortical and corticothalamic interactions as the spindle activity spreads (Steriade, 2006). Therefore, their reduction suggests an impairment in trans-thalamic cortico-cortical interactions (Vukadinovic, 2011). Sleep spindles are generated by the thalamus, but they are initiated and synchronized by the cortex (Destexhe et al., 1998). In schizophrenia, both the spindle number and coherence have been found to be reduced (Wamsley et al., 2012) suggesting that both (1) corticothalamic mechanisms for their initiation and synchronization as well as (2) intrinsic thalamic mechanisms for their generation are impaired in this illness. As sleep spindles are modulated by aminergic and cholinergic subcortical inputs (Steriade, 2006), their reduction also points to a dysfunction of those systems in this illness as well. Importantly, sleep spindle reduction in schizophrenia was not found to be secondary to antipsychotic medication use (Ferrarelli et al., 2010) and their amount was found to be negatively correlated with positive symptoms of schizophrenia (Ferrarelli et al., 2010; Wamsley et al., 2012). This latter finding suggests that the pathologic mechanism responsible for their reduction also has significance for the genesis of psychosis.

Thus, it should be noted that schizophrenia is associated with a reduction in a thalamocortical network-dependent sleep brain rhythm (i.e., sleep spindles). In contrast, the illness is also associated with an increase in delta activity in awake individuals with

schizophrenia (Boutros et al., 2008; Venables et al., 2009). Delta rhythm (1–4 Hz) normally occurs during the deep stages of slow wave sleep (SWS) (stages 3 and 4). Moreover, Venables et al. (2009) also found that the increase in delta is positively correlated with disease severity. Zhang et al. (2012) have argued that as delta is normally seen during SWS, its occurrence during wakefulness in schizophrenia points to a pathophysiologic process that disrupts normal thalamic function and may be involved in the genesis of psychosis.

In our opinion, the reported increase in delta rhythm in schizophrenia during wakefulness is also suggestive of thalamocortical disconnection, as this rhythm has been found to be enhanced by surgical removal of the thalamus (Villablanca and Salinas-Zeballos, 1972). Additionally, neurophysiological recordings from neocortical tissue slabs documented emergence of a rhythm that resembled delta (Ball et al., 1977). These results together suggest that delta rhythm in the cortex can function in relative isolation from the thalamus (Bazhenov and Timofeev, 2006; Buzsaki, 2006). Namely, delta has been classified as an intrinsic rhythm (Bazhenov and Timofeev, 2006; Buzsaki, 2006), which tends not to rely on the interactions between excitatory and inhibitory neurons within a population (like network-dependent rhythms such as sleep spindles do), but rather have been found to function in relative isolation. It should, however, also be noted that this view of slow cortical rhythms may be an oversimplification, as the emergence of slow (<1 Hz) rhythm of NREM sleep has been found to rely on a dynamic interactions between the cortex and the thalamus (for a review see Crunelli and Hughes, 2010). Also, there is evidence that delta rhythm is an active phenomenon that is to some extent disrupted by N-methyl D-aspartate receptor (NMDAR) antagonism, as well

as with pharmacological inactivation of the MD thalamic nucleus (Kiss et al., 2011).

Nonwithstanding these important findings, it should be noted for the purposes of this review that schizophrenia is associated with a reduction of a network-dependent rhythm that requires intact cortico-thalamo-cortical interactions (i.e., sleep spindles) and with an increase of an intrinsic rhythm that has in some studies been found to be enhanced by thalamocortical disconnection. As both reported abnormalities are related to the severity of the illness, we argue that the proposed concept of cortico-thalamo-cortical disconnection is crucial for the genesis of psychosis, and that looking at brain rhythm abnormalities in this illness is a useful approach to understanding the pathophysiology of schizophrenia.

4. Cannabis worsens structural thalamic abnormalities in schizophrenia

In a recent longitudinal study by Welch et al. (2011a), it was found that cannabis use by individuals at high familial risk of psychosis is associated with thalamic volume loss. Unfortunately, in this study the authors were not able to determine if some thalamic nuclei were affected more than others due to insufficient resolution (Welch, personal communication, 2011). However, in a different study by the same group, frequent cannabis use in individuals at risk of psychosis was reported to be associated with third ventricle enlargement, possibly implicating tissue loss in the anterior medial region of the thalamus that includes the MD nucleus (Welch et al., 2011b). Thus, from this it may be inferred that the increased risk of schizophrenia with cannabis exposure could be mediated by its effects on the thalamus, and in particular, the HO MD nucleus. By extension, as the HO thalamic nuclei are concerned with trans-thalamic cortico-cortical interactions, we argue that cannabis exposure increases the risk of psychosis in vulnerable individuals by exacerbating the structural abnormalities that are related to the impairment in such interactions. In the following sections, we will review certain aspects of thalamic neurophysiology such as its ability to display two different modes of neuronal firing (tonic and burst modes) as well as the potential impact of cannabis on the ability of the thalamus to display corticothalamically induced burst firing.

5. Thalamic burst firing and schizophrenia

The concept of the thalamic post-inhibitory rebound burst firing mode, as opposed to the tonic firing mode, has been described by Jahnsen and Llinas (1984) (also see Sherman, 2001). In short, when in a relatively depolarized state, thalamocortical neurons fire tonically or, in other words, proportionally to their excitatory inputs. However, when thalamic neurons are hyperpolarized by their inhibitory neuromodulatory inputs for approximately 100 ms, low threshold calcium channels (T-type calcium channels) become de-inactivated, which causes influx of calcium ions into the neuron. This event is termed low threshold calcium spike (LTS). The T-type calcium channels are found in the neuronal cell body and in the dendrites and open at substantially more negative membrane potentials compared to other calcium channels (L-, N- and P/Q-type) (Perez-Reyes, 2003). As a consequence of the LTS, thalamic neurons respond with a rebound burst of action potentials when subsequently further depolarized by excitatory signals. This mode of responding to excitatory signals is termed the burst firing mode. Importantly, the two firing modes occur in different contexts.

The tonic mode predominates in wakefulness while the burst mode occurs to a greater extent in non-rapid eye movement sleep (NREM), during which it tends to appear rhythmically. Namely, thalamocortical neurons are hyperpolarized during NREM sleep

relative to their membrane potentials during wakefulness when corticothalamic inputs are more active (Buzsaki, 2006). During SWS, cortical pyramidal neurons undergo slow oscillations, which consist of rhythmic shifts in their membrane potentials between UP states, when they are relatively depolarized, and DOWN states of relative hyperpolarization (Steriade, 2006). These oscillations occur at about 1 Hz. As UP states are near the spike threshold, populations of cortical cells are more likely to fire a volley of action potentials, which in turn launches spindle activity in the thalamus, or more specifically, in the thalamic reticular nucleus (TRN) (Steriade, 2006). The TRN is a thalamic structure that lies adjacent to the rest of the thalamus and is composed of a thin layer of GABA-ergic neurons, which provide some of the inhibitory inputs to the thalamus and regulate the thalamic firing mode (Sherman and Guillery, 2006). The TRN is innervated by branches of corticothalamic and thalamocortical axons that pass through this structure. The cortical UP states induce the switch to the burst firing mode in some TRN neurons, which in turn hyperpolarize their thalamocortical target neurons and thereby cause them to likewise switch to the burst firing mode. Subsequently, the spindle activity spreads involving increasingly larger areas of the thalamus and cortex with each cycle of firing. Importantly, delta rhythm also involves thalamic post-inhibitory rebound burst firing but at lower frequencies (Buzsaki, 2006).

We argue here that the reduction in sleep spindle amount and their coherence in schizophrenia (Wamsley et al., 2012), informs our understanding of the pathophysiology of schizophrenia: (1) it provides further evidence for malfunctioning of the cortico-thalamo-cortical circuits as interactions between the thalamus and the cortex are required for spindle initiation and synchronization (Destexhe et al., 1998). (2) It suggests a reduced ability of the thalamus to display the burst firing mode in response to high levels of cortical activity. The cortical UP states during SWS have been found to dynamically resemble activated cortical states during wakefulness (Destexhe et al., 2007), and therefore what occurs during spindle initiation may have relevance for what occurs during wakefulness. The two arguments together may in turn account for the emergence of the pathologic delta rhythm in wakefulness in individuals with schizophrenia (Boutros et al., 2008; Venables et al., 2009), as some reports in the literature suggest that delta rhythm emerges when the thalamus and cortex are relatively disconnected, such as in athalamic animals (Villablanca and Salinas-Zeballos, 1972). Thus, both brain rhythm abnormalities reported in schizophrenia may be two sides of the same coin, which is the proposed hypofunctioning of cortico-thalamo-cortical circuits. This issue may in turn be related to the proposed NMDAR hypoactivity in this illness. Indeed, blocking NMDARs with ketamine has been found to cause an increase in delta rhythm and to reduce spindle activity (Buzsaki, 1991). In summary, we propose that schizophrenia involves a disorder of the thalamic burst firing with a reduction in cortically induced burst firing, which then in turn leads to the emergence of delta during wakefulness. The pathologic delta rhythm then further exacerbates thalamic dysfunction (Zhang et al., 2012).

It has been found that spindle and delta activities have an inverse relation during NREM sleep (Uchida et al., 1991). For example, sleep deprivation in humans has been found to be associated with an increase in slow wave activity, including delta rhythm, with concomitant reduction in spindle activity (Duk et al., 1993). The frequency at which thalamic burst firing occurs (whether at delta or spindle frequency) depends on the membrane hyperpolarization of thalamic neurons, with more hyperpolarized membrane potentials (−80 mV) favoring delta rhythm, while less hyperpolarized potentials (−65 mV) favor spindle activity (Steriade and Amzica, 1998). As both sleep spindles and delta involve T-type calcium channels, one way to interpret their inverse relationship

is that the two rhythms “compete” (Buzsaki, 2006) for the same “hardware” (i.e., T-type channels). This concept of competition between the two brain rhythms has theoretical significance for our understanding of psychosis, as it raises the question of what occurs in individuals with schizophrenia during wakefulness in the presence of the pathologic delta rhythm. Namely, the pathologic intrinsically generated delta rhythm during wakefulness in schizophrenia may “outcompete” corticothalamically induced burst firing in the thalamus, which in turn could have relevance for our understanding of perceptual abnormalities in psychosis.

6. Cortically induced thalamic burst firing and perception

The occurrence of the thalamic burst firing is not strictly restricted to NREM sleep and can also occur in awake cats (Guido and Weyand, 1995), rodents (Fanselow et al., 2001; Swadlow and Gusev, 2001), primates (Ramcharan et al., 2000 and 2005) and humans (Radhakrishnan et al., 1999). In awake, active and unanesthetized primates, the extent of the burst firing was found to be dramatically greater in the HO nuclei (Ramcharan et al., 2005). More specifically, the animals in this experiment were engaging in a visual fixation task, which required that they are in an attentive state. As the HO thalamic nuclei relay cortical inputs to other cortical areas, this suggests that burst firing has a role in trans-thalamic cortico-cortical communication, as well as in the related concept of internal motor monitoring as a central function of those nuclei. More specifically, the HO nuclei tended to display the burst firing mode when the animal was presented with novel stimuli, which presumably required some form of exploratory behavior.

According to Krahe and Gabbiani (2004), burst firing in response to sensory inputs relies on intrinsic neuronal mechanisms (such as availability of the T-type calcium channels) as well as on inputs from higher centers involved in motor control (e.g., cortex). Thus, the shift to burst firing in the thalamus may be involved in the adjustment of thalamocortical signal transmission in accordance with ongoing exploratory behavior of an animal. In addition to their proposal that burst firing occurs in accordance with behavior, Krahe and Gabbiani (2004) further point out that burst firing in sensory systems encodes behaviorally relevant stimuli, which suggests that this pattern of responding to sensory inputs is crucial for the perception–action cycle. Indeed, thalamic burst firing has been found to dynamically enhance sensory responsiveness in accordance with certain ongoing exploratory behaviors (Krahe and Gabbiani, 2004) such as whisker twitching in rodents (Fanselow et al., 2001; Nicolelis and Fanselow, 2002). The proposed function of thalamic burst firing mode during some of these exploratory behaviors is to improve the signal to noise ratio and to alert the cortex to behaviorally salient stimuli (Sherman and Guillery, 2006).

Destexhe and Sejnowski (2002) found that corticothalamic inputs are crucial for the initiation of thalamic burst firing and that they thereby adjust thalamocortical sensitivity. Importantly, when in the burst firing mode, thalamocortical relay neurons respond to sensory stimuli non-linearly (Sherman and Guillery, 2006), strongly activate cortical circuits (Swadlow and Gusev, 2001), and therefore, have the ability to reconfigure larger thalamocortical networks (Kim et al., 1997). All of these findings together are consistent with a role for the thalamic burst firing in perception (Krahe and Gabbiani, 2004). Therefore, the proposed reduced ability of the thalamus in schizophrenia to display corticothalamically induced burst firing, as suggested by the reported reductions in sleep spindles described above, would be expected to be associated with perceptual abnormalities, as well as with a relative uncoupling of the perception–action cycle, which has been noted to be characteristic of schizophrenia (Feinberg, 2011; Fuster, 2008).

It should be noted, however, that the view that post-inhibitory rebound burst firing in the thalamus has a role in perception is controversial (Steriade, 2001). The alternative view is that the main function of this firing mode is in sleep, during which it serves to effectively isolate the cortex from the thalamus thereby exerting a sleep-protective effect (Steriade, 2006). Consistent with this view, the occurrence of the burst firing mode in wakefulness is thought to be pathological, as it is thought to disrupt thalamocortical information flow (thalamocortical dysrhythmia), which in turn contributes to disorders such as schizophrenia (Llinas et al., 1999). The influential and important concept of thalamocortical dysrhythmia (TCD) does not account for the findings described above, that rebound burst firing indeed occurs in awake and attentive primates (Ramcharan et al., 2005). Our understanding of the valuable concept of TCD is that the occurrence of the thalamic burst firing mode in wakefulness can indeed disrupt thalamocortical circuits if generated intrinsically (i.e., delta rhythm in wakefulness). In contrast, cortically initiated thalamic burst firing has been proposed to be a part of a mechanism whereby the firing mode is dynamically adjusted to behavior with the effect of increasing the signal to noise ratio (Krahe and Gabbiani, 2004).

7. The significance of T-type calcium channels for thalamic neurophysiology

Wei et al. (2011) found that relay neurons in the pulvinar of the tree shrew are more likely to display the burst firing mode in comparison to the LGN neurons. They also suggested that this finding is secondary to increased density of T-type calcium channels in the pulvinar. The increased density of the T-type calcium channels, and subsequent increased calcium currents in the pulvinar, may act to amplify descending cortical inputs and help integrate them with ascending inputs (Wei et al., 2011). Thus, the ability of the thalamus to support trans-thalamic cortico-cortical communication may, apart from the structural integrity of the HO nuclei, also depend on the availability of T-type calcium channels to support cortically induced thalamic burst firing mode (Ramcharan et al., 2005). It follows that in any such scenario, the anatomical distribution and the functioning of T-type calcium channels are of importance (Wei et al., 2011).

There are three subtypes of the human T-type calcium channels, namely $Ca_v3.1$, $Ca_v3.3$ and $Ca_v3.2$, which encode the pore forming α -subunit of the T-type channels with highly varied CNS tissue distribution (Astori et al., 2011; Iftinca, 2011; Snutch and David, 2006; Talley et al., 1999). All three subtypes are co-expressed in thalamic structures with $Ca_v3.3$ showing the highest regional specificity (Fig. 1A) (Astori et al., 2011; Talley et al., 1999). The $Ca_v3.3$ mRNA and protein are abundant in GABAergic cells of the TRN, in particular in their distal dendrites, which receive the majority of corticothalamic inputs to this thalamic structure (Liu and Jones, 1999). The T-type calcium channels in distal dendrites of the TRN neurons ($Ca_v3.3$) are thought to amplify corticothalamic inputs and enable cortical modulation of the thalamic firing mode (Crandall et al., 2010). The excitatory thalamocortical neurons are not immunopositive for $Ca_v3.3$ but contain the other two subtypes ($Ca_v3.1$ and $Ca_v3.2$) with a preponderance of $Ca_v3.1$ (Astori et al., 2011). Astori et al. (2011) also showed that $Ca_v3.3$ channels are crucial for TRN function and for sleep spindles genesis.

8. Exogenous cannabinoids and T-type calcium channels

Accumulating experimental data suggests that exogenous cannabinoids may directly affect T-type calcium channels and thereby exacerbate the proposed dysregulation of thalamocortical

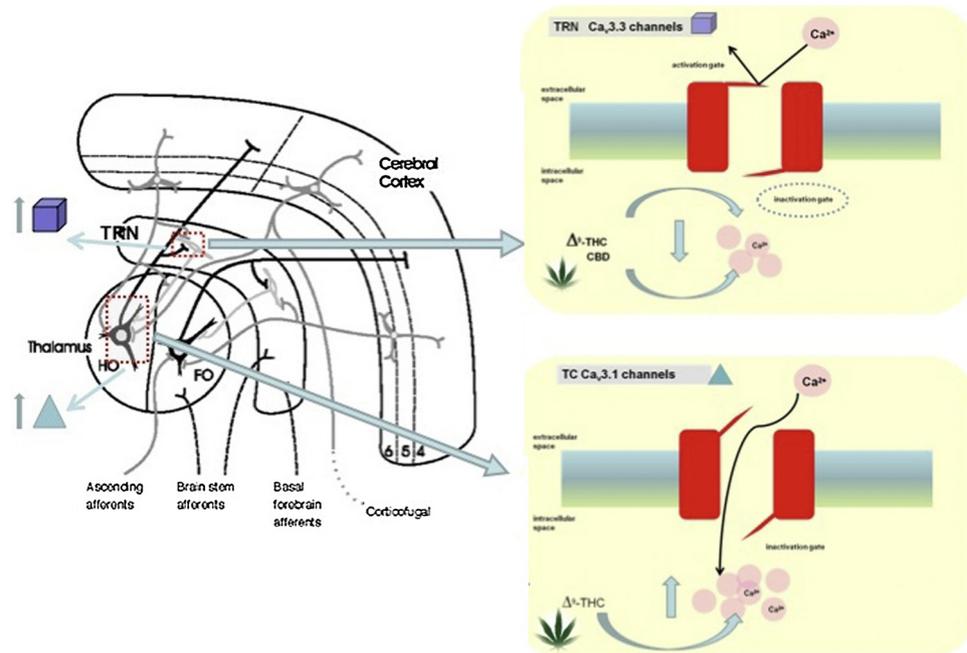


Fig. 2. The cortex, the TRN and the thalamus (first order and higher order nuclei) are depicted left (adapted with permission from Guillery et al., 1998). The HO thalamic nuclei are innervated by layer V cortical inputs, which also provide corticofugal projections to lower motor centers. The TRN is innervated by branches of thalamocortical and layer VI corticothalamic passing through it. Right side of the figure: an illustration of the effects of the two major constituents of *Cannabis sativa*, namely Δ^9 THC and CBD on $Ca_v3.1$ (triangle) and $Ca_v3.3$ (cube) subtypes is shown. The overall effect of both exogenous cannabinoids on the TRN neurons, where the expression of $Ca_v3.3$ channels is predominant, is likely to cause a hyperpolarizing shift and hence will also be inhibitory of the TRN inhibition of the TC neurons. Ross et al. (2008) suggested that the hyperpolarizing shift in steady state inactivation of the channels (as emphasized by the circled inactivation gate of the channel in upper right) most likely represents their major mechanism of inhibition. This has the effect of reducing the number of channels that can open when the cell is depolarized. In the case of CBD, this effect in the TRN might be counterbalanced by its equally inhibitory effect on the $Ca_v3.1$ channels in the excitatory TC neurons themselves. Intriguingly, Δ^9 THC specific longitudinal modulatory effects on the two subtypes of channels ($Ca_v3.1$ and $Ca_v3.2$) of which $Ca_v3.1$ is more prevalently expressed on the TC neurons, are likely to result in their longer term depolarizing shift and increased intracellular calcium (see lower right). Thus, the final impact of Δ^9 THC is likely to decrease the ability of the thalamus to respond in the burst firing mode in response to corticothalamic inputs, while the effect of CBD on the burst firing mode may be more neutral.

firing in schizophrenia (Fig. 2) (Snutch and David, 2006; Ross et al., 2008). Namely, the two major ingredients of cannabis, Δ^9 THC and CBD, were shown to inhibit all three subtypes of the human T-type calcium channels at pharmacologically relevant concentrations in cell cultures (Caulfield and Brown, 1992; Ross et al., 2008). Ross et al. (2008) also found that Δ^9 THC and CBD inhibit T-type channels in mouse sensory neurons. These effects were found to be substantial and independent of the cannabinoid receptors. At the holding potential of -70 mV, both Δ^9 THC and CBD, at concentrations comparable to those achieved in the brain after smoking a marijuana cigarette, inhibited 50% of the peak calcium current through the channels during the subsequent depolarization. It was suggested that the hyperpolarizing shift in steady state inactivation of the channels (Fig. 2) most likely represents their major mechanism of inhibition (Ross et al., 2008). This has the effect of reducing the number of channels that can open when the cell is depolarized.

Intriguingly, Ross et al. (2008) also showed that several important aspects of T-type calcium channel inhibition by CBD and Δ^9 THC differed. Firstly, Δ^9 THC effect on $Ca_v3.1$ was completely use-dependent with greater inhibition at higher currents used to depolarize the cells. The inhibition by Δ^9 THC was also strongly dependent on the voltage at which the cells were held. Its inhibitory effect was minimal when currents were evoked from the strongly hyperpolarized membrane potentials. On the other hand, CBD inhibitory effect on this channel subtype was not frequency or voltage dependent. Secondly, Δ^9 THC showed dramatic modulatory effects on $Ca_v3.1$ and $Ca_v3.2$ channels, but not on the $Ca_v3.3$ subtype, by causing a substantial slowing of channel inactivation from an open state and de-activation following repolarization. This effect was readily evident at concentrations below those that

substantially inhibited the peak channel current, and unlike its inhibition, it occurred rapidly and was not voltage-dependent. Again, this apparent stabilization of the channels by Δ^9 THC, probably longitudinally resulting in increased intracellular calcium and increased neuronal excitability, was not observed with CBD.

In view of these findings regarding the differential effects of CBD and Δ^9 THC on the three subtypes of the T-type calcium channels, we can make certain inferences regarding how these two agents impact thalamic neuropathophysiology in schizophrenia. Firstly, CBD was found to block T-type calcium channels even at very hyperpolarized membrane potentials, which in thalamocortical and TRN neurons favor the emergence of delta rhythm. Thus, CBD is more likely than Δ^9 THC to interfere with the pathological delta rhythm in schizophrenia, which could be related to its antipsychotic potential noted earlier in this review (Zuardi et al., 2006). Interestingly, Uslaner et al. (2012) reported that a novel T-type calcium channel antagonist (TTA-A2) has potential antipsychotic effect in animal models of psychosis. This drug has not yet been tested in humans. Importantly, however, Dreyfus et al. (2010) demonstrated that T-type calcium channels are expressed in the thalamus in sufficient numbers to enable the occurrence of LTS in response to inhibitory inputs even when the majority of the channels were blocked. Thus, TTA-A2 may exert its antipsychotic-like effects in animal behavioral studies by blocking enough T-type calcium channels to diminish the pathological intrinsically-generated thalamic burst firing (Uslaner et al., 2012) but, importantly, the ability of the thalamus to display the burst firing mode in response to its inhibitory inputs (such as those from the TRN) may be preserved (Dreyfus et al., 2010). Thus, the antipsychotic potential of CBD and the reported antipsychotic-like

effects of TTA-A2 in animal models may be related, as both may be mediated by their effects on T-type channels. It is of note that these channels are not present only in the thalamus. Therefore, we cannot exclude the possibility that these compounds exert their behavioral effects by affecting some other parts of the brain in addition to the thalamus.

In contrast, Δ^9 THC has not been found to block the T-type calcium channels at more hyperpolarized potentials, which, as already mentioned, favor the emergence of delta rhythm (Buzsaki, 2006). Therefore, Δ^9 THC may not interfere with the generation of delta rhythm in the thalamus. Additionally, as already mentioned, it was found to slow channel inactivation from an open state as well as de-activation following repolarization. In other words, it was found to stabilize open states of the channels resulting in greater calcium influx longitudinally, which could then lead to increased excitability of thalamocortical neurons and a reduction in their ability to display the burst firing mode in response to corticothalamic inputs. Moreover, the longitudinally increased intracellular calcium may lead to excitotoxicity and could contribute to neuronal loss in the HO nuclei in chronic cannabis users who are at risk of schizophrenia. In summary, the effect of CBD in schizophrenia may be to reduce the pathological delta rhythm by blocking a substantial portion of T-type calcium channels in the thalamus. Importantly, as long as some of the channels remain available, the ability of the thalamus to generate the burst firing mode in response to corticothalamic inputs to the TRN would be preserved. In contrast, the longitudinal increase in intracellular calcium in thalamocortical cells by Δ^9 THC may impair the generation of the thalamic burst firing mode. Thus, Δ^9 THC via its effects on T-type calcium channels, may interfere with the ability of the HO nuclei to support trans-thalamic cortico-cortical communication by compromising their structural integrity as well as by inhibiting the thalamic burst firing. Finally, a recent report implicated the T-type calcium channels in the generation of tonic firing in the thalamus (Deluze et al., 2012), which raises the issue that the inhibition of these channels by Δ^9 THC and CBD could also interfere with this firing mode.

It should be noted that the endogenous cannabinoids (i.e., anandamide) may also inhibit T-type calcium channels independently of cannabinoid receptors (Snutch and David, 2006; Ross et al., 2008). However, anandamide, apart from the similar effects to that of CBD, additionally also accelerates Ca_v3 open channel inactivation. This probably results in a significant decrease in the available window current and may in effect underlie some of its protective effects in cases of abnormally high neuronal spiking activity (Marsicano et al., 2003). Indeed, it has been purported that endocannabinoid system may work as an on-demand defense signaling system, and that increased production of endocannabinoids occurs during neuronal depolarization. In accord, cannabinoids have been reported as neuroprotective in certain models of neurotoxicity.

9. Conclusion and directions for further research

A growing body of in vitro, animal and human data suggests that cannabis exposure may worsen some thalamic abnormalities noted in schizophrenia. Namely, this illness is associated with reduced thalamic volumes (Andrews et al., 2006; Brickman et al., 2004; Byne et al., 2009; Danos et al., 2003), with the HO nuclei (i.e., MD, pulvinar) affected to a greater extent compared with the FO nuclei (Byne et al., 2009). Cannabis exposure in individuals who are genetically at higher risk of psychosis has also been associated with reduced thalamic volumes (Welch et al., 2011a,b). Clearly, more research is needed to determine which thalamic nuclei are affected by cannabis use. As the HO thalamic nuclei are implicated in internal motor monitoring (Sherman and Guillery, 2011), it is proposed

here that cannabis may worsen psychosis by exacerbating the structural brain abnormalities that may be related to the noted impaired central internal motor monitoring and source-monitoring deficits in schizophrenia (Vukadinovic, 2011). Moreover, the inhibition of T-type Ca^{2+} channels by the exogenous cannabinoids raises the possibility that cannabis exposure also dysregulates the mode of thalamocortical firing (burst versus tonic). This may in turn, as discussed earlier, also interfere with trans-thalamic cortico-cortical communication (Ramcharan et al., 2005) and thereby increase psychosis risk.

This review is the first article to propose that the exogenous cannabinoids may indeed differentially interfere with T-type calcium channel subtypes in the thalamus. This, we propose, may have important implications for our understanding of the mechanisms involved in the increased risk of psychosis in cannabis users. Furthermore, the theoretical constructs depicted here may shed crucial light on varied psychotogenic effects of different strains of street cannabis (Bhattacharyya et al., 2009; Di Forti et al., 2009; Morgan et al., 2010). More specifically, we argue that Δ^9 THC impairs trans-thalamic cortico-cortical interactions by longitudinally increasing the excitability of thalamocortical neurons, which in turn interferes with the generation of the burst firing and has the potential to result in excitotoxicity. Therefore, the cannabis strains that have a higher proportion of Δ^9 THC would be expected to confer a greater risk of psychosis. In “weaker” strains of cannabis that contain a higher proportion of CBD, CBD could be argued to have a neutral or possibly even protective effect, perhaps via its competition with Δ^9 THC for the channel sites in the thalamus or possibly by its interference of the delta rhythm generation.

Finally, any ensuing disruption of the corticothalamically induced burst firing in the thalamus may also diminish trans-thalamic cortico-cortical communication and lead to a relative disconnection between different associated cortical regions. In genetically predisposed individuals, this could worsen or lead to further deficits seen in schizophrenia. The scenario we propose here is tentative but nonetheless raises important questions for future research. In terms of basic research, it would be interesting to determine if Δ^9 THC and CBD do indeed have the effects on T-type calcium channels described by Ross et al. (2008) in thalamic slices. This could also be indirectly tested by examining the effects of different cannabis strains intoxication on EEG recordings. To our knowledge, current literature on the effects of cannabis on sleep does not contain reports on how cannabis intoxication may affect sleep spindle or delta activities. We suggest that the varied effects that Δ^9 THC and CBD have on Ca_v3 subtypes make them intriguing candidates for lead molecules in probing the functional domains and the physiological impacts of these channels.

One potential weakness of the model presented in this review is that we discussed acute effects of exogenous cannabinoids on the T-type calcium channels and extrapolated how these effects could lead to psychosis, which is a long-term risk with continued cannabis use, particularly in adolescence. However, there are some reports in the literature that cannabis use, and in particular Δ^9 THC, induced psychotic symptoms acutely as well as longitudinally (for a review see Bhattacharyya and McGuire, 2012). It is possible that the Δ^9 THC interference with the function of T-type calcium channels (Ross et al., 2008) in the thalamus leads to acute pro-psychotic effects, while chronically elevated calcium levels in thalamic neurons in regular cannabis users leads to excitotoxicity and neuronal cell loss in the HO thalamic nuclei, thereby conferring the long-term psychosis risk.

Another potential limitation of the above discussion is that we only discussed potential consequences of the effects of the exogenous cannabinoids on T-type calcium channels in the thalamus. The T-type calcium channels are present ubiquitously in the brain

including the cortex (Perez-Reyes, 2003), and their chronic inhibition in regular cannabis users during brain development might alter cortical network activity in the long-term, and perhaps lead to up or down regulation of these channels in young cannabis users. In keeping with this, it has been shown that a marked adaptive plasticity occurs in the TRN in response to cortical injury leading to augmented excitatory input in uninjured corticothalamic fibers (Paz et al., 2010). Moreover, sleep spindles, resulting from an interplay of actions of these channels, are known to contribute to brain plasticity both in adulthood and during development, and hence, any profound chronic effect on their genesis should be matter of concern (Fogel and Smith, 2011; Khazipov and Luhmann, 2006). In this context, it is important that a recent longitudinal study by Meier et al. (2012) found that adolescent-onset cannabis use was associated with marked long-term cognitive decline. Interestingly sleep spindles are statistically related to intelligence (Fogel and Smith, 2011), which raises the possibility that the effects of Δ^9 THC on T-type calcium channels in the brain have relevance not only to our understanding of psychosis but also of cannabis-induced cognitive decline.

Finally, it has to be recognized that there are other models that attempt to explain the role of cannabis in the etiology of schizophrenia (summarized by Bhattacharyya and McGuire, 2012). These models focus on the effects of exogenous cannabinoids on cannabinoid 1 receptor (CB1) at which Δ^9 THC may act as a partial agonist. This, however, has not been demonstrated in humans. It is thought that Δ^9 THC has (1) direct inhibitory effects on GABAergic neurotransmission and/or (2) indirect enhancing effects on dopaminergic neurotransmission. It should be noted that the models that emphasize interactions between Δ^9 THC and CB1 also to some extent implicate the thalamus, as cannabinoid receptors are expressed in this structure in humans (Glass et al., 1997). More specifically, Glass et al. (1997) demonstrated that the expression of cannabinoid receptors is higher in the HO thalamic nuclei compared with the rest of the thalamus. Regarding possible effects of exogenous cannabinoids on brain rhythms, Hajos et al. (2000) found that CB1 stimulation in the hippocampus reduced GABA release and thereby also reduced the power of hippocampal network oscillations.

In summary, in this review we presented a model that attempts to provide neurobiological explanation for the role of cannabis in the etiology of psychosis by proposing that the reported effects of the two main exogenous cannabinoids on T-type calcium channels alter the function of cortico-thalamo-cortical circuits. Other proposed models for the pro-psychotic effects of cannabis have emphasized the role of the activity of Δ^9 THC on the CB1 receptor in the brain. One novel aspect presented in this review is that the role of cannabis in schizophrenia may at least in part be related to receptor-independent mechanisms. The purpose of this review is to encourage further research in this direction.

Conflict of interest

The authors do not have any conflict of interest to report. The authors apologize to all the colleagues whose outstanding work could not be cited due to space limitations.

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