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$GABA_B$ receptors: modulation of thalamocortical dynamics and synaptic plasticity

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Abstract—$GABA_B$-receptors ($GABA_B$-Rs) are metabotropic, G protein-coupled receptors for the neurotransmitter GABA. Their activation induces slow inhibitory control of the neuronal excitability mediated by pre- and postsynaptic inhibition. Presynaptically $GABA_B$-Rs reduce GABA and glutamate release inhibiting presynaptic Ca^{2+} channels in both inhibitory and excitatory synapses while postsynaptic $GABA_B$-Rs induce robust slow hyperpolarization by the activation of K^+ channels. $GABA_B$-Rs are activated by non-synaptic or volume transmission, which requires high levels of GABA release, either by the simultaneous discharge of GABAergic interneurons or very intense discharges in the thalamus or by means of the activation of a neurogliaform interneurons in the cortex. The main receptor subunits $GABA_{B1a}$, $GABA_{B1b}$ and $GABA_{B2}$ are strongly expressed in neurons and glial cells throughout the central nervous system and $GABA_B$-R activation is related to many neuronal processes such as the modulation of rhythmic activity in several brain regions. In the thalamus, $GABA_B$-Rs modulate the generation of the main thalamic rhythm, spindle waves. In the cerebral cortex, $GABA_B$-Rs also modulate the most prominent emergent oscillatory activity—slow oscillations—as well as faster oscillations like gamma frequency. Further, recent studies evaluating the complexity expressed by the cortical network, a parameter associated with consciousness levels, have found that $GABA_B$-Rs enhance this complexity, while their blockade decreases it. This review summarizes the current results on how the activation of $GABA_B$-Rs affects the interchange of information between brain areas by controlling rhythmicity as well as synaptic plasticity.

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SYNAPTIC TRANSMISSION THROUGH METABOTROPIC $GABA_B$ RECEPTORS IN THALAMUS AND CORTEX

GABAergic neurons are the major inhibitory cell type in the mammalian brain and exhibit a wide variety of morphological and physiological properties. The activation of GABAergic neurons can inhibit postsynaptic target cells through increases in Cl^- conductance, mediated by the $GABA_A$ receptor, and increases in K^+ conductance, mediated by the $GABA_B$ receptor ($GABA_B$-R). $GABA_B$-Rs are widely distributed in the central nervous system and have been found at both excitatory and inhibitory neurons (Ulrich and Bettler, 2007) as well as in other types of neurons such as dopaminergic (Boyes and Bolam, 2003) or striatal cholinergic interneurons (Yung et al., 1999; Waldvogel et al., 2004). In addition, $GABA_B$-Rs are expressed in glial cells (López-Bendito et al., 2004); in fact most of the neurons in the central nervous system contain $GABA_B$-Rs (Steiger et al., 2004). $GABA_B$-Rs are G protein-coupled receptors for the neurotransmitter GABA. Interestingly, $GABA_B$-Rs are similar in structure to (and in the same receptor family as) metabotropic glutamate receptors (Kaupmann et al., 1997). $GABA_B$-Rs are expressed pre- and postsynaptically, controlling the release of the neurotransmitter and the excitability of the receiving neurons respectively. Initially, $GABA_B$-Rs were found to be insensitive to the bicuculline component of inhibitory responses, which was activated by L-baclofen (Bowery et al., 1980). For many years it was thought that the $GABA_B$-R family would be found to consist of numerous receptor subtypes, due to the variety in responses obtained with the current agonist and antagonist. However, further investigations demonstrated that there are only two receptor subtypes, $GABA_{B1a}$ and $GABA_{B1b}$, both of them combined with $GABA_{B2}$ subunits to form hetero-

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meric $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors (Jones et al., 1998; Kaupmann et al., 1998; White et al., 1998). These receptor units are produced by a different promoter form by the $GABA_B1$ gene (Bischoff et al., 1999; Steiger et al., 2004), and they are different in their N-terminal ectodomain by a pair of sushi repeats only in $GABA_{B1a}$ (Blein et al., 2004). Both isoforms are found in different locations; $GABA_{B1a}$ are mainly found in presynaptic terminals, where they control neurotransmitter release (Vigot et al., 2006), which depending on the specific type of synapse, excitatory or inhibitory, may inhibit or disinhibit respectively. The presynaptic action of $GABA_B$-Rs inhibiting glutamate release occurs in many areas of the central nervous system (Willcockson et al., 1984; Dutar and Nicoll, 1988; Huston et al., 1995; Emri et al., 1996; Lin et al., 1996) and most probably in all cortical areas (Deisz and Prince, 1989; Kang, 1995; Ramoa and Sur, 1996; Ziakopoulos et al., 2000). $GABA_B$-R-mediated inhibition requires the activation of the adenylyl cyclase/protein kinase A second messenger pathway, through the triggering of Gαi/o-type G proteins and liberation of Gβγ subunits, activating G protein-coupled inward-rectifying K^+ channels and inhibition of voltage-gated Ca^{2+} channels (Bettler et al., 2004) (Figure 1). Presynaptic $GABA_B$-Rs, usually the $GABA_{B1a}$ subunit, inhibit neurotransmitter release through the inhibition of voltage-gated Ca^{2+} channels (Gassmann et al., 2004). Presynaptic $GABA_B$-Rs are termed autoreceptors when controlling GABA release, and heteroreceptors when inhibiting other types of neurotransmitter (Figure 1). Often, by means of the activation of presynaptic $GABA_B$-Rs, GABA decreases glutamate release mainly by blocking voltage-sensitive Ca^{2+} channels and also by the modulation of synaptic vesicle priming (Maguire et al., 1989; Mintz and Bean, 1993; Sakaba and Neher, 2003). Postsynaptically, $GABA_{B1b}$ are located in the dendritic spines, controlling K^+ channels that are involved the postsynaptic inhibition (Pérez-Garci et al., 2006), generating slow inhibitory potentials by the activation of Kir3-type K^+ channels (Luscher et al., 1997) (Figure 1). $GABA_B$-Rs also decrease dendritic Ca^{2+} by blocking voltage gate calcium channels in the distal dendrites (Chalifoux and Carter, 2011).

$GABA_B$-Rs are broadly distributed along the CNS and can generate a large combination of outcomes, making $GABA_B$-Rs a key element for wide dynamic control of synaptic transmission. Thus, in order to understand the role of $GABA_B$-Rs in synaptic transmission, it is crucial to identify the specific components underlying the studied circuit, as well as the pre- and postsynaptic location of the $GABA_B$-Rs. Moreover, in addition to the structural components, the dynamic properties of synaptic transmission should be taken into account, including the different regimens of spontaneous brain activity and the previous history of synaptic activity at the related synapses.

One early idea about the function of $GABA_B$-Rs was that they controlled slow changes in neuronal excitability. In most cases, the activation of $GABA_B$ autoreceptors needs a strong activation to become active, by means of synchronous activity or repetitive stimulation. This was clearly demonstrated in the thalamus (Kim et al., 1997) and also in the hippocampus (Scanziani, 2000). In line with this evidence, it has been shown that $GABA_B$-Rs are located distal to the release sites that require GABA volume transmission (Bettler and Tiao, 2006). This is true for most brain areas; however, more recent evidence has demonstrated a very important exception:

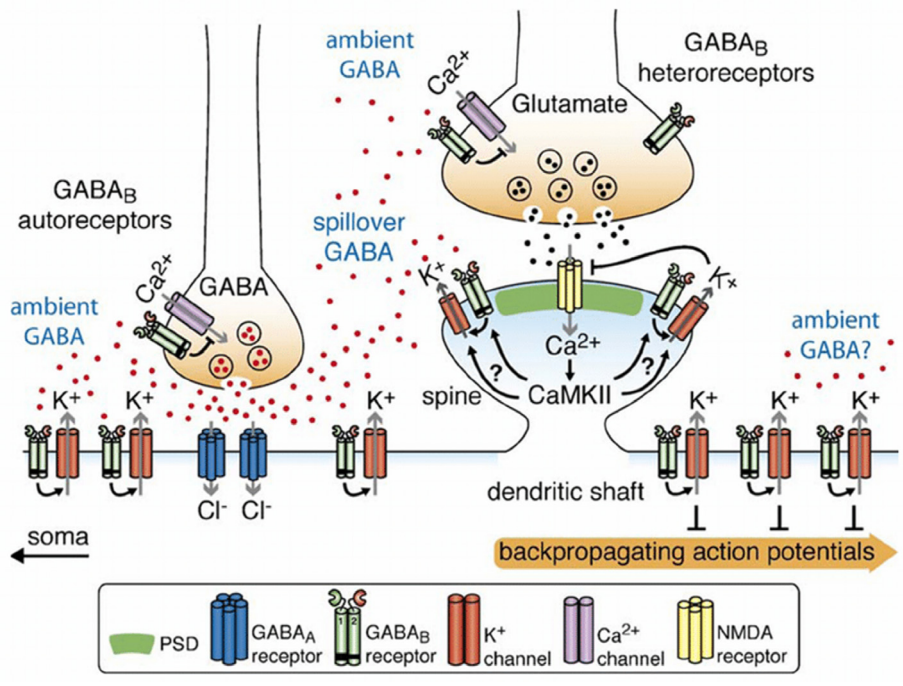

Figure 1. Distribution and role of $GABA_B$-Rs. $GABA_B$-Rs are located presynaptically on extrasynaptic membranes. Presynaptic $GABA_B$-Rs prevent neurotransmitter release by down-regulating the activity of voltage-sensitive Ca^{2+} channels or inhibiting the release machinery. $GABA_B$ autoreceptors inhibit the release of GABA, whereas $GABA_B$ heteroreceptors inhibit the release of glutamate and several other neurotransmitters. $GABA_B$-Rs are also expressed postsynaptically. They induce sIPSCs by activating Kir3-type K^+ -channels, which hyperpolarizes the membrane, favors voltage-sensitive Mg^{2+} block of NMDA receptors and shunts excitatory currents. $GABA_B$-Rs in spines and dendrites are expressed to regulate the excitability of the network and to counteract excess excitation during population oscillation and epileptiform activity. Dendritic $GABA_B$-Rs inhibit back propagating action potentials through activation of K^+ -channels. During high-frequency transmission GABA depresses its own release by an action on $GABA_B$ autoreceptors, which permits sufficient NMDA receptor activation for the induction of LTP. Reprinted from ''Chapter 19: $GABA_B$ Receptor and Absence Epilepsy," by Hua A. Han, Miguel A. Cortez, and O. Carter Snead in *Jasper's Basic Mechanisms of the Epilepsies (4th edn)*, Jeffrey Noebels, Massimo Avoli, Michael Rogawski, Richard Olsen, and Antonio Delgado-Escueta (eds), Oxford University Press: Oxford. Reused with permission.

in the cerebral cortex $GABA_B$-Rs can be strongly activated by the activity of neurogliaform interneurons. In fact, it was shown that a single action potential of the neurogliaform cells releases enough GABA to generate a slow inhibition mediated by $GABA_A$ and $GABA_B$ receptor activation (Tamas et al., 2003). This type of interneuron targets both dendritic spines of pyramidal neurons (Tamas et al., 2003) and different types of interneurons (Oláh et al., 2007).

Neurogliaform neurons were initially described by Ramon y Cajal (Ramon y Cajal, 1922). They are located in all cortical layers, but those in layer 1 are of special functional relevance in the long-lasting inhibition induced by $GABA_B$ that was demonstrated to elucidate interhemispheric inhibition in mice (Palmer et al., 2012). This type of indirect long-lasting inhibition is used to explain how one hemisphere imposes its dominance during a specific sensory or motor process. The activation of the layer 1 neurons by callosal transmission induced a delayed inhibition by hundreds of milliseconds in the layer 5 pyramidal neurons. This type of inhibition occurred in the distal dendrites, induced by the GABA release activating $GABA_{B1b}$ receptors on the postsynaptic pyramidal neurons (Palmer et al., 2012) and suggests the activation of neurogliaform interneurons induces it. Interestingly, beyond the callosal transmission, this evidence shows that the activation of layer 1 inhibits pyramidal neurons for hundreds of milliseconds. In fact, previous studies demonstrated that the stimulation of distal dendritic regions of pyramidal neurons recruited a $GABA_B$-R-mediated inhibition (Dutar and Nicoll, 1988; Pérez-Garci et al., 2006). In addition to the synaptic transmission and the sensory processing, this long-lasting inhibition mediated by $GABA_B$-Rs has been proposed as a mechanism to control brain states. In an elegant *in vitro* study in active cortical slices, Mann and colleges analyzed how electrical stimulation of layer 1 could trigger a transition from Up to Down states (see below). This interesting result demonstrates that persistent cortical activity can be switched off by the inhibition mediated by $GABA_B$-R activation (Mann et al., 2009). Additional studies showed the specific role for two types of $GABA_B$-Rs, $GABA_{B1a}$ and $GABA_{B1b}$. Using mouse lines of knockout phenotypes for both $GABA_B$-Rs, Mann et al. demonstrated that the transition to the Down state previously described is only mediated by the activation of the $GABA_{B1b}$ subunit, and not by the $GABA_{B1a}$. This result strongly suggests a postsynaptic mechanism underlying the modulation of transition states.

Role of $GABA_B$ receptors in synaptic plasticity in the thalamocortical loop

In order to understand the role of $GABA_B$-Rs in synaptic plasticity, it is crucial to identify the specific components underlying the studied circuit, as well as the pre- and postsynaptic location of the $GABA_B$-Rs. Moreover, in addition to the structural components, the dynamic properties of synaptic transmission should be taken into account, including the different regimes of spontaneous brain activity and the previous history of synaptic activity at related synapses. This section summarizes the knowledge of the $GABA_B$-Rs mediating synaptic transmission and plasticity in thalamus and cortex.

As mentioned above, cortical inhibition mediated by the activation of $GABA_B$-Rs plays a crucial role regulating neuronal excitability and plasticity. $GABA_B$-Rs contribute to the regulation of inhibition presynaptically, through the autoinhibition of inhibitory interneurons, and postsynaptically, by means of long-lasting inhibitory postsynaptic potentials (Morrisett et al., 1991; Olpe et al., 1993; Deisz, 1999; Stäubli et al., 1999). Many early studies tried to understand the role of the $GABA_B$-Rs in synaptic plasticity by pharmacological blockade of $GABA_B$-Rs, which often generated contradictory results showing either an increase (Olpe and Karlsson, 1990; Olpe et al., 1993; Stäubli et al., 1999) or a reduction of long-term potentiation (Davies et al., 1991; Mott and Lewis, 1991). These apparently conflicting results may be explained by a leading effect of $GABA_B$-R modulation on either $GABA_B$-R-mediated inhibitory postsynaptic potentials or autoinhibition of neurotransmission through $GABA_A$-Rs (Stäubli et al., 1999). In the cerebral cortex, as well as in other brain regions, presynaptic $GABA_B$-Rs inhibit glutamate release (Kang, 1995; Ramoa and Sur, 1996). Experiments in thalamocortical slices described the effect of the $GABA_B$-Rs mediating either intracortical or thalamo-cortical excitatory synaptic transmission. The application of the $GABA_B$-R agonist baclofen reduced the amplitude of intracortical EPSPs, also inducing a slight increase in the paired-pulse ratio, but without effecting thalamocortical transmission (Gil et al., 1997). Similar selective suppression of intrinsic but not afferent fiber synaptic transmission by baclofen was also previously described in the piriform cortex (Tang and Hasselmo, 1994). These results suggest that cortical GABA release selectively suppresses specific pathways by activating presynaptic $GABA_B$-Rs. This type of input selection mediated by $GABA_B$-Rs was also demonstrated in the perirhinal cortex. The electrical stimulation in either the entorhinal or temporal cortex induced paired pulse depression (PPD) in the perirhinal cortex, during interpulse interval from 100 to 1000 milliseconds. PPD was mediated by GABA spilling over onto excitatory synapses, activating presynaptic $GABA_B$-Rs in glutamatergic terminals. $GABA_B$-R-mediated PPD was greater when the temporal cortex was stimulated, suggesting that this pathway has a preferred role controlling the firing and synaptic plasticity of the perirhinal cortex (Ziakopoulos et al., 2000).

As mentioned previously, postsynaptically $GABA_B$-Rs activate K^+ channels and also directly inhibit Ca^{2+} mediated dendritic spikes, throughout the dendritic arbor, in cortical and hippocampal pyramidal neurons (Pérez-Garci et al., 2006; Larkum et al., 2007; Chalifoux and Carter, 2011). Ca^{2+} influx via voltage-sensitive Ca^{2+}-channels has an important role as an intracellular messenger, activating intracellular signaling cascades that are ultimately responsible for altered synaptic efficacy (Grover and Teyler, 1990; Huang and Malenka, 1993). Therefore, $GABA_B$-Rs could modulate long-term plasticity by direct action on dendritic spines. *In vivo* experiments also studied the functions of $GABA_B$-R

blockage on short-term synaptic plasticity. Jia and colleagues described the impact of the blockage of $GABA_B$-Rs in the thalamocortical visual pathway (Jia et al., 2004). They did so by means of electrical stimulation in the dLGN and recordings in V1 before and after iontophoresis of 2-hydroxy-saclofen. The authors described that both paired pulse and short-term depression were reduced by blocking $GABA_B$-Rs.

$GABA_B$-Rs are also involved in the induction of long-term potentiation at visual cortical inhibitory synapses (Komatsu, 1996). Moreover, $GABA_B$-R activation is necessary for the induction of inhibitory LTP at fast-spiking cell to pyramidal cell synapses, which converts LTP to LTD at convergent excitatory pyramidal cell synapses (Wang and Maffei, 2014). Following these results and given that long-term plasticity changes are related to the deprived eye responses, $GABA_B$-Rs have also been related to the plasticity of the critical period for ocular dominance in the primary visual cortex of cats. During the critical period, monocular deprivation induces an ocular dominance shift. In juvenile animals, the application of the $GABA_B$-R agonist enhanced the plasticity facilitating the ocular dominance shift, while the $GABA_B$-R antagonist impaired it. However, in adult cats the infusion of the same neuromodulators did not induce any significant impact on the ocular dominance shift. These results evidence the role of $GABA_B$-Rs in juvenile ocular dominance plasticity (Cai et al., 2017).

$GABA_B$ RECEPTORS AND EMERGENT RHYTHMIC PATTERNS: THALAMIC ACTIVITY

Thalamocortical rhythms have a relevant role in the triggering of brain rhythms across different brain states (Llinas and Ribary, 1993; Steriade et al., 1993b). The thalamic reticular nucleus (TRN), and its interaction with the thalamic nuclei, has been proposed as a central modulator of corticothalamic feedback that could modulate sleep states through the modulation of brain rhythms (McCormick and Bal, 1997; Steriade, 2000; Fernandez et al., 2018). The TRN is a nucleus with the shape of a shell around the dorsal thalamus that is formed solely by GABAergic neurons. These neurons are bursty, oscillatory neurons (Kim et al., 1997; Fogerson and Huguenard, 2016) that have large axonal arborizations that profusely innervate thalamic nuclei (Jones, 2012). Furthermore, interlaminar neurons in the visual thalamus are formed by neurons that are equivalent anatomically, electrophysiologically, pharmacologically, anatomically, immunocytochemically, and functionally to the TRN (perigeniculate) neurons (Sanchez-Vives et al., 1996) (Figure 2C). The involvement of the TRN, and thus of inhibitory interneurons, in the control of brain states, is such that GABAergic synaptic transmission has been proposed to be critical for anesthetic drugs to induce unconscious states, by enhancing the effects of TRN activity (Brown et al., 2011). Furthermore, some seizure activity such as absence seizures and its associated spike and wave activity also originate in the thalamus (Hosford et al., 1992; Labate et al., 2005; see below). Alteration of TRN conductances decreases EEG sleep rhythms (Cueni et al., 2008; Espinosa et al., 2008) and other studies demonstrate that the TRN, and its interaction with thalamocortical neurons, initiates sleep spindles (Figure 2A, B) (Steriade et al., 1987; Von Krosigk et al., 1993; Bazhenov et al., 2000; Halassa et al., 2011; Bartho et al., 2014). Optogenetic studies have shown that TRN may modulate arousal states through selective inhibition of thalamic activity, facilitating the onset of slow waves (Lewis et al., 2015). But, to what extent is the GABAergic action of TRN neurons mediated by $GABA_B$-Rs? We will refer here to studies in the TRN section around the visual thalamus, which is called the perigeniculate nucleus (PGN), and which maintains the characteristics of TRN. PGN neurons innervate thalamocortical neurons (excitatory) reciprocally (Figure 2C): on their way to the cortex, the axons of the thalamocortical neurons cross the PGN, leaving collaterals at this level. In return, the PGN cells densely innervate the relay cells. In this way, a network of reciprocal interactions between excitatory and inhibitory neurons is established (Kim et al., 1997). When these neurons fire in the bursty mode, this reciprocal innervation results in the generation of spindle waves (Figure 2B) (Von Krosigk et al., 1993). The inhibition deactivates low threshold calcium current (Jahnsen and Llinás, 1984), inducing the rebound burst in thalamocortical cells that results in a cycle of inhibition and bursting that then excites PGN cells (Figure 2A,B), which also burst and further inhibit thalamocortical neurons, which then results in the 7–14 Hz spindle wave (Von Krosigk et al., 1993; McCormick and Bal, 1997). The inhibitory contribution to this cycle relies only on $GABA_A$-Rs, and the blockade of $GABA_B$-Rs does not affect spindle waves (Bal et al., 1995a, 1995b).

Thus, when are $GABA_B$-Rs activated? PGN neurons inhibit not only thalamocortical neurons, but also inhibit each other laterally, both through $GABA_A$ and $GABA_B$ receptors (Figure 3) (Sanchez-Vives et al., 1997). This is equivalent to what happens between TRN neurons (Shu and McCormick, 2002). When PGN neurons are disinhibited by blocking $GABA_A$ receptors, they fire longer bursts of high-frequency action potentials. Under these conditions, it was observed that the inhibition exerted over thalamocortical neurons (Sanchez-Vives and McCormick, 1997) and also over other PGN neurons (Sanchez-Vives et al., 1997) was mediated through $GABA_B$-Rs (Figure 2B). Given that $GABA_B$-Rs have a slower time course, the recurrent circuit involving thalamocortical and PGN cells, oscillated at a highly synchronized, slower pace of 3 Hz (Figure 2B). (Sanchez-Vives and McCormick, 1997), a pattern that is highly similar to that generated during absence seizures (Hosford et al., 1992). Therefore, the switch of network activity from relying on $GABA_A$ towards relying on $GABA_B$-Rs has a large impact on the oscillatory rhythm emerging from the thalamocortical network and the activation of $GABA_B$-Rs may be particularly important to the generation of some forms of generalized spike-and-wave seizures.

As mentioned above, in order for PGN cells to activate $GABA_B$-Rs they should be disinhibited in order for them to have longer and more intense firing patterns. This was highly suggestive that the activation of $GABA_B$-Rs

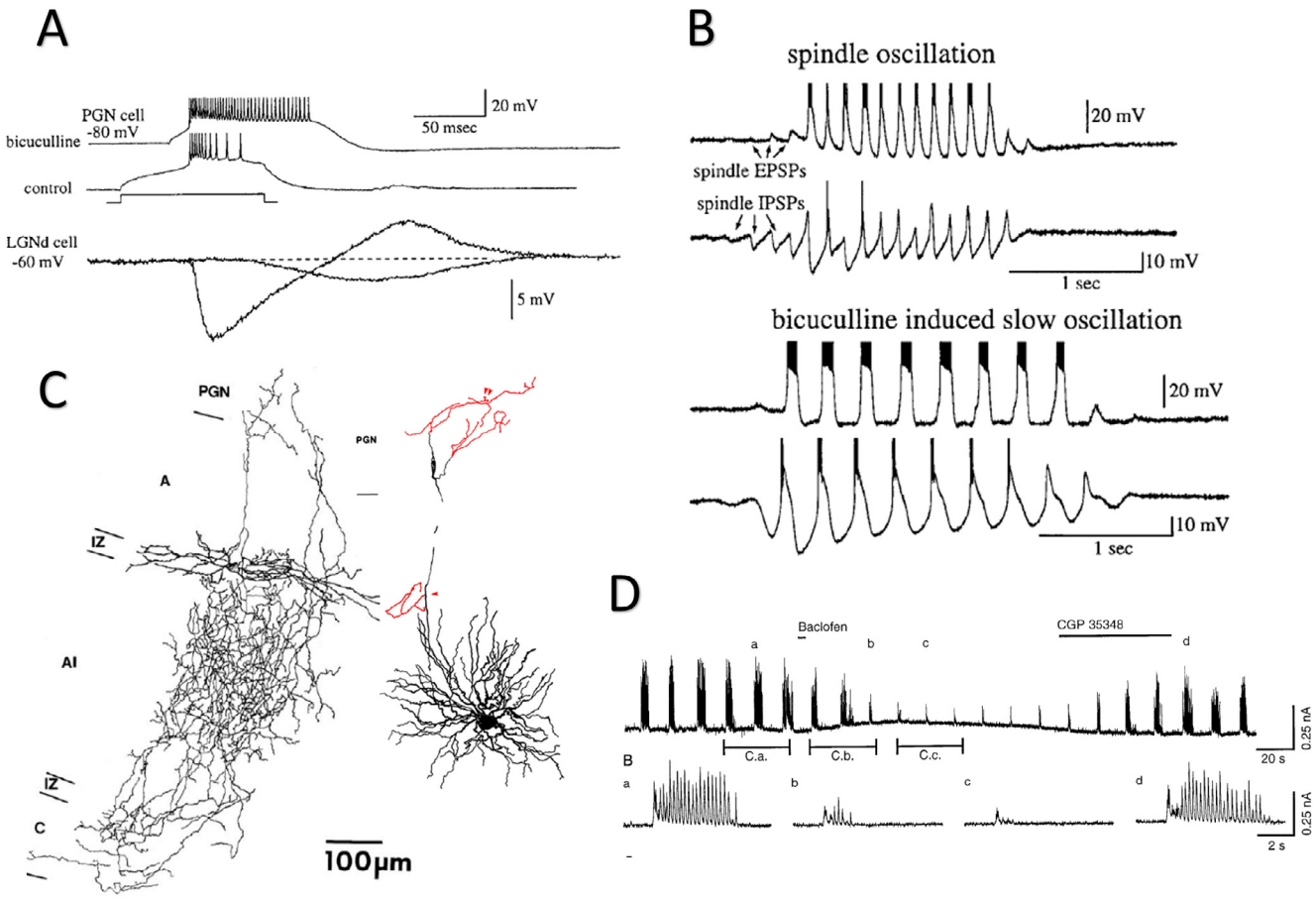

Figure 2. Pre- and postsynaptic $GABA_B$-R modulation of thalamic activity patterns. (**A**) Activation of a burst of action potentials in the PGN cell before and after bath application of bicuculline. (**B**) Spontaneous generation of a spindle wave is associated with repetitive burst firing in the PGN neuron and the occurrence of repetitive IPSPs in the LGNd cell. The IPSPs are generated by the activity of this PGN cell as well as others. After bath application of bicuculline, the geniculate slice spontaneously generates abnormal oscillations during which the PGN neuron generates prolonged high-frequency burst discharges. Source: Kim, U. et al. (1997) Functional dynamics of GABAergic inhibition in the thalamus. *Science* 278(5335):130-4. Reused with permission. (**C**) The cell body and dendrites located in the A-A1 interlaminar zone (IZ). The axon densely innervated lamina A1 and also innervated lamina C. One branch of the axon passed through lamina A and into the PGN. Source: Sanchez-Vives et al. (1996). Are the interlaminar zones of the ferret dorsal lateral geniculate nucleus actually part of the perigeniculate nucleus? *Journal of Neuroscience* 16(19): 5923-5941. Reused with permission. (**D**) (**Top**) IPSCs recorded in a thalamocortical cell with a microelectrode filled with 2M CsAc and held at 259 mV. Each barrage of IPSCs represents the generation of a spindle wave and was evoked with the local application of glutamate in the PGN. Application of baclofen (100 mM in the micropipette) results in a large reduction in the amplitude of the initial evoked IPSC as well as the generation of spindle wave-associated IPSCs. Local application of CGP 35348 reversed these effects. (**Bottom**) Expansion of spindle wave-associated IPSCs before and after application of baclofen and after recovery with application of CGP 35348.

required a larger release of GABA, generally accepting that several GABAergic neurons should contribute in order for the extrasynaptic $GABA_B$-Rs to be reached. However, Kim et al. (1997) demonstrated that the same single PGN neuron could indeed activate both $GABA_A$ and $GABA_B$, with the difference that the activation of $GABA_A$ and $GABA_B$ required prolonged burst firing. Further, $GABA_B$-R activation had a delay of 52 ms with respect to the activation of $GABA_A$-Rs (Kim et al., 1997), which could be due to the properties of G-protein-mediated events that are the intermediaries between receptor binding and K^+ channel opening or the location of receptors as extrasynaptic receptors (Figure 1) (Mody et al., 1994). Similar features to those described in the thalamus for $GABA_B$-Rs are described in the hippocampus for $GABA_A$/$GABA_B$ activation and their impact on rhythmicity (Scanziani, 2000). In more recent years, it has been proposed that the activation of $GABA_B$-Rs even contributes to the generation of thalamic spindle oscillations (Ulrich et al., 2018), modulates thalamocortical excitation of cortical inhibitory and excitatory neurons, and participates in the processing of sensory information in the barrel cortex (Porter and Nieves, 2004). Moreover, stimulation of $GABA_B$-Rs has been found to be effective in cortical seizure-like activity suppression (Chang et al., 2017).

$GABA_B$-Rs are also present on the presynaptic terminals of both GABAergic neurons (Figure 3E) as well as thalamocortical connections (Figure 2D), and the activation of these receptors results in the reduction of neurotransmitter release (Ulrich and Huguenard, 1996; Sanchez-Vives et al., 1997b). These results suggest that the activation of presynaptic $GABA_B$-Rs also plays an important role in the regulation of intrathalamic activity.

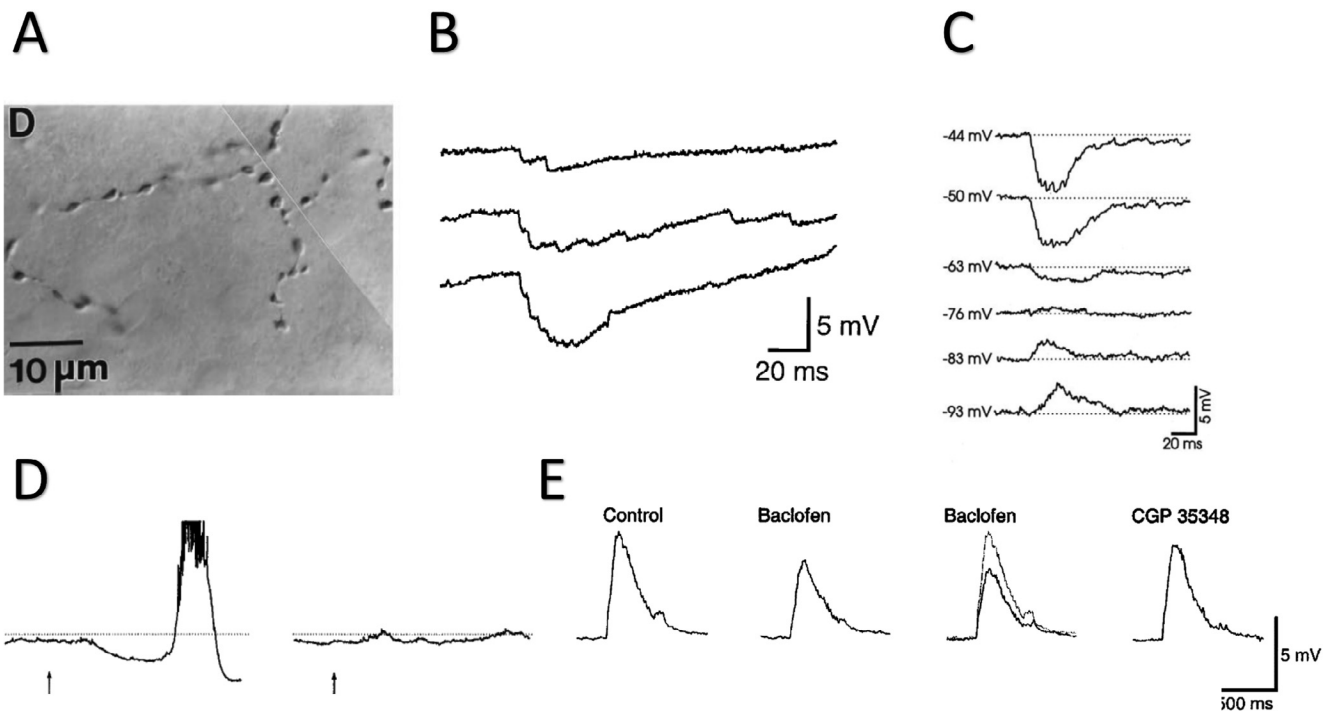

Figure 3. Lateral $GABA_A$ and $GABA_B$ (pre and postsynaptic) inhibition between inhibitory, perigeniculate neurons in the thalamus. (**A**) Higher power photomicrograph with Nomarski optics of boutons in the PGN cell. (**B**) Example of barrage of IPSPs that spontaneously occur in PGN neurons and presumably result from the burst discharge of single PGN neurons. (**C**) Evoked barrage of IPSPs in a neighboring PGN cell. Each compound IPSP is composed of several presumed unitary IPSPs. (**D**) Local application of bicuculline (400 mM in micropipette) reduces but does not completely block evoked IPSP. (**E**) Evoked EPSPs recorded in a PGN cell. The local application of baclofen results in a reduction in the amplitude of these evoked EPSPs. The local application of CGP 34348 reverses this action of baclofen. Source: Sanchez-Vives et al. (1997). Inhibitory interactions between perigeniculate GABAergic neurons. *Journal of Neuroscience* 17(22): 8894-8908. Reused with permission.

$GABA_B$ RECEPTORS AND EMERGENT RHYTHMIC PATTERNS: CORTICAL ACTIVITY

The cortical network can synchronize its activity in different rhythmic patterns ranging from infraslow to ultrafast activity (Buzsaki and Draguhn, 2004). However, of all these possible frequencies, there is a prominent frequency that dominates the dynamics of the cortical emergent activity during sleep and pathological states: slow wave activity, driven by slow oscillations. Slow oscillations emerge from the recurrent interaction between cortical neurons, making them a network phenomenon (Steriade et al., 1993c). During the active periods, or Up states, neocortical neurons (both excitatory and inhibitory) are depolarized, receive barrages of synaptic inputs and fire action potentials. During the ensuing Down states, neurons remain hyperpolarized and the synaptic activity is almost silent. Cortical recordings from different species agree on the leading role of infragranular layers—in particular layer 5—in the initiation of Up states (Sanchez-Vives and McCormick, 2000; Sakata and Harris, 2009; Chauvette et al., 2010). During Up states, the activity expresses coherent oscillations at high frequencies in the beta (15–30 Hz) and gamma (30–90 Hz) range (Cunningham et al., 2004; Compte et al., 2008). This phenomenon is multiscale such that slow oscillations display similar characteristics whether they are recorded from the intact cortex of a sleeping human or from a small piece of cortex in a plate. It has been proposed that fluctuations of Up- and Down-states—the origin of the slow waves—is the "default" intrinsic pattern of cortical activity (Sanchez-Vives and Mattia, 2014; Sanchez-Vives et al., 2017). The cortex defaults to slow-wave activity due to changes in neuromodulation, as in sleep (Steriade et al., 2001; Riedner et al., 2007) or due to changes in the excitatory/inhibitory balance as in deep anesthesia (Steriade, Conteras et al., 1993a; Chauvette et al., 2011) , or as a consequence of structural lesions, as when a cortical gyrus is physically isolated by cutting the underlying white matter (Timofeev and Steriade, 1996) or in a cortical slab (Timofeev et al., 2000).

A key element in the balance and control of either spontaneous emergent or evoked cortical activity is the relationship between excitation and inhibition. Both excitatory and inhibitory neurons fire during Up states as originally described by Steriade et al (1993). Conductance measurements during Up states reveal that the weights of excitation and inhibition are well-balanced *in vivo* (Haider et al., 2006) and similarly *in vitro* (Shu et al., 2003) as has been proposed in a cortical computational model (Compte et al., 2003). Changes in excitatory and inhibitory conductance *in vitro* reveal that both increases and decreases at the beginning/end of Up states occur in close association with each other (Shu et al., 2003; Zucca et al, 2017). Indeed, the timing of individual excitatory and inhibitory synaptic events also reveals a remarkable coincidence in the accumulation of both excitatory and inhibitory synaptic events during the

rise of an Up state, both *in vitro* and *in vivo*, although it is 1.4 times faster *in vivo* (Compte et al., 2009). A similar coincidence between the timing of excitatory and inhibitory events also occurs at the termination of the Up state. Such interlocking in time of excitation and inhibition is also found in simultaneous recordings of nearby pairs of cortical neurons (Okun and Lampl, 2008). When measuring excitatory versus inhibitory conductances, both have been found to be high at the beginning of the Up state and tend to progressively decrease, but their ratio remains constant and close to 1 in both anesthetized and *in vitro* preparations (Shu et al., 2003; Haider et al., 2006). However, other studies report that the inhibitory conductance is much larger than the excitatory conductance during Up states in natural sleep (Rudolph et al., 2007).

Mechanisms of termination of the Up states

Several mechanisms have been proposed that could account for the termination of Up states. They include: arrival of excitation (Shu et al., 2003; Haider et al., 2006), synaptic depression (Bazhenov et al., 2002, but see Benita et al 2012), thalamic disfacilitation (Contreras et al., 1996), activation of K^+ currents (Sanchez-Vives and McCormick, 2000; Compte et al., 2003) or extracellular K^+ dynamics (Fröhlich et al., 2006). The time course of the slow afterhyperpolarization observed in intracellular recordings during Down states (e.g. fig. 7C in Contreras et al., 1996; Sanchez-Vives and McCormick, 2000; Sanchez-Vives et al, 2010), suggests that slow K^+ currents can contribute to the termination of Up states and maintenance of Down states. Different mechanisms involving K^+ currents have been proposed, including ATP-dependent K^+ current (Cunningham et al., 2006) and Ca^{2+} and Na^+-dependent K^+ currents (Sanchez-Vives and McCormick, 2000). Slow K^+-mediated afterhyperpolarizations are blocked by neurotransmitters (acetylcholine, noradrenaline) that control the transition from sleep to awake states (Schwindt et al., 1988; Brumberg et al., 2000), providing a mechanism for stopping the bistability when entering the awake state (D'Andola et al, 2017).

$GABA_B$-Rs activation (Parga and Abbott, 2007; Mann et al., 2009; Wang et al., 2010; Craig et al., 2013; Perez-Zabalza et al., 2020) is a plausible mechanism involved in the termination of Up states. More than one of the mentioned mechanisms most probably interact and contribute to the termination of the Up-to-Down state transition. Mann and colleagues analyzed how electrical stimulation of layer 1 could trigger a transition from Up to Down states. This result suggested that persistent cortical activity can be switched off by $GABA_B$-R-mediated inhibition (Mann et al., 2009) (Figure 4A). Additional studies showed a specific role of the two types of $GABA_B$-Rs—$GABA_{B1a}$ and $GABA_{B1b}$. Using mouse lines of knockout phenotypes for both $GABA_B$-Rs, it was found that the transition to the Down state was mediated by the activation of the $GABA_{B1b}$ subunit, and not by the $GABA_{B1a}$, thus suggesting a postsynaptic mechanism (Craig et al., 2013). Modelling work has also suggested that $GABA_B$ dynamics have the correct timescale to contribute to this

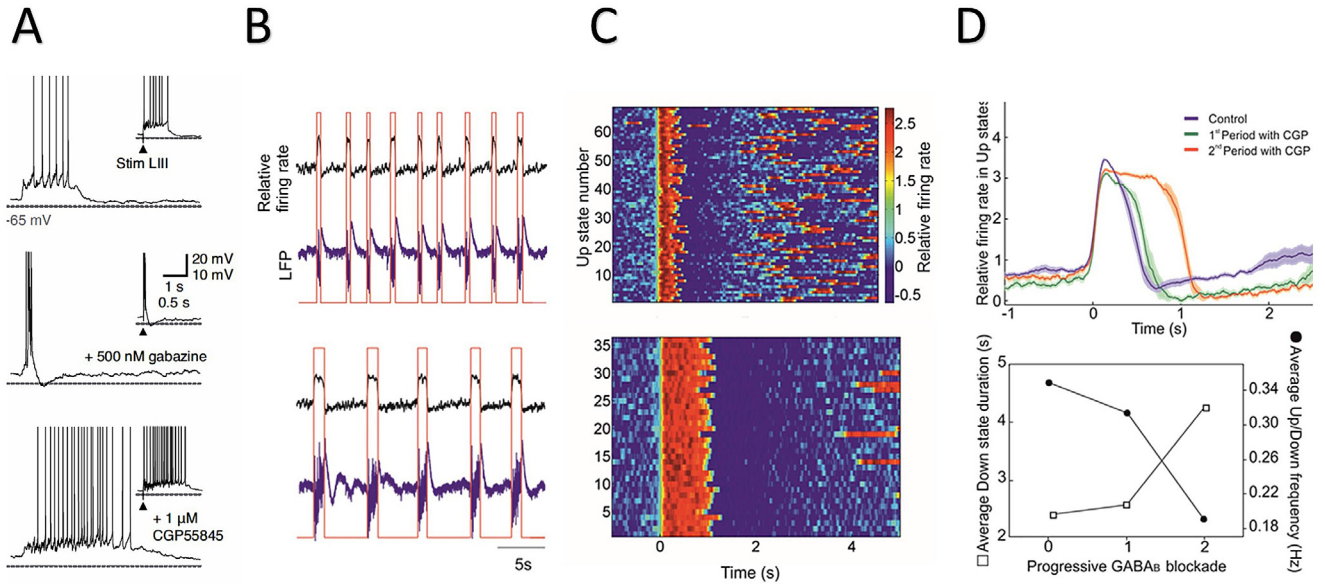

Figure 4. $GABA_B$-R modulation of cortical Up and Down states (**A**) Whole-cell recordings in control (**top**), 500 nM gabazine (**middle**), and 1M CGP55845 (**bottom**). Insets show equivalent Up states triggered by stimulation in the same cells. Source: Mann et al. (2009). Distinct roles of $GABA_A$ and $GABA_B$ receptors in balancing and terminating persistent cortical activity. *Journal of Neuroscience*, *29*(23), 7513-7518. Reused with permission. (**B**) Raw signal (blue trace), relative firing rate (black trace) and detected Up and Down states (red trace) under control activity (**top**) and after application of 200 µM CGP 35348 (**bottom**). (**C**) Raster plots of the relative firing rate are represented for control activity and for 200 µM CGP 35348 corresponding to the ones in (B). (**D**) (**Top**) Average relative firing rate for Up states during the control and 200 µM CGP 35348 corresponding to the ones in (A). The shadow corresponds to the s.e.m. (**Bottom**) Down-state duration decreases whereas the oscillation frequency increases. Source: Perez-Zabalza et al.(2020) Modulation of cortical slow oscillatory rhythm by $GABA_B$ receptors: an *in vitro* experimental and computational study. *J Physiol.* doi: 10.1113/JP279476. Reused with permission.

Down state termination process (Parga and Abbott, 2007) and that they could interact with firing rate adaptation to modulate the generation of slow oscillations. Indeed, Perez-Zabalza et al. (2020), not only found a significant elongation of Up states when $GABA_B$-Rs were blocked (Figure 4), but different cortical dynamics during the slow oscillatory regime: subsequent Down states were most commonly (75% cases) elongated (typical) -and thus the oscillatory frequency decreased (Figure 4B, C)-, while the remaining cases were shortened (atypical), therefore affecting the whole oscillatory cycle. Interestingly $GABA_B$-R blockade also strikingly increased the regularity of the slow oscillation dynamics, revealing that the activation of $GABA_B$-Rs introduces irregularity, variability and dynamical richness in the spontaneous slow oscilations (Perez-Zabalza et al., 2020). In this study it was also found that the Down-to-Up transition slope, which corresponds to the recruitment of the local network (Reig et al., 2010; Sanchez-Vives et al., 2010), was not affected by $GABA_B$-R blockade. Interestingly, the Up-to-Down (downward) transition slope was significantly decreased, further supporting the role of $GABA_B$-Rs in the termination of Up states.

$GABA_B$-Modulation Of Cortical Complexity

Throughout different brain states, cortical units interact in different ways resulting in a variety of cortical dynamics that are accompanied by switches of behavioral states (Gervasoni et al., 2004). Such cortical dynamics result from reciprocal interactions between excitatory and inhibitory cortical units, depolarizing simultaneously, but the most active inhibitory populations vary during different brain states (Gentet et al., 2010). During awake states, cortical activity is characterized by complex patterns of causal interactions, whereas this complexity collapses in deep sleep or anesthesia (Steriade, 2006). The study of the mechanisms that modulate the emergence of complex brain states is critical to the development of new methodologies to detect brain state and consciousness levels (i.e., during anesthesia or in brain-injured patients) and promote state transitions and recovery of function. The study of cortical complexity can be approached from the paradigm of the balance between segregation and integration of cortical activity, defined as brain complexity (Tononi, 2004). Different methods have been used to quantify brain complexity in humans. The Perturbational

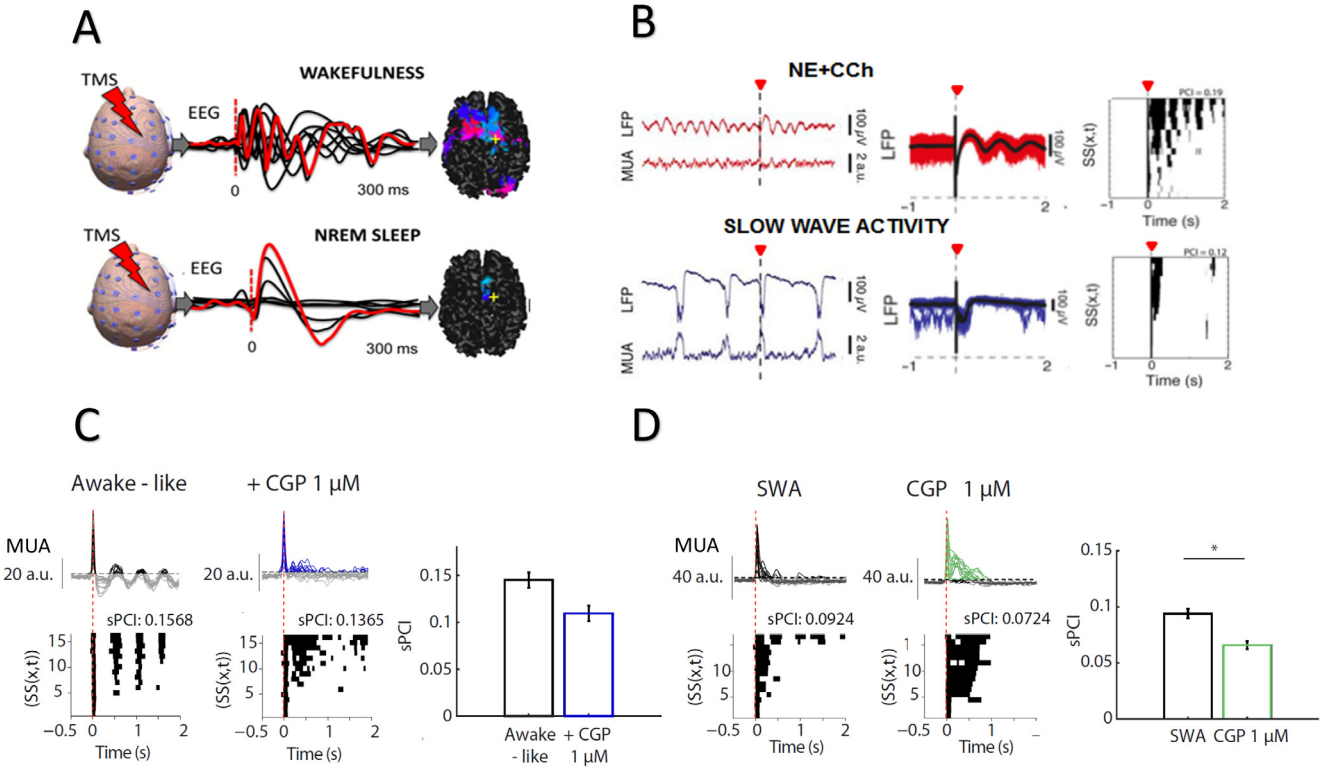

Figure 5. $GABA_B$-R modulation of cortical complexity. Brain complexity measured in human using PCI, can be studied in isolated cortical slices *in vitro*. (**A**) Average of EEG responses following TMS (Red) and maximum current sources (color-coded according to their activation latency: light blue, 0 ms; red, 300 ms). Yellow cross: TMS target on the cortex. Source: Sanchez-Vives et al. (2017). Shaping the default activity pattern of the cortical network. *Neuron* 94:993–1001. Reused with permission. Originally modified from Pigorini et al. (2015) *Neuroimage* 112, 105-113. (**B**) Spontaneous emerging activity in isolated cortical slices, (**top**) Local Field Potential (LFP) and (**bottom**) Multiunit activity (MUA) under bath application of 50 µM NE and 0.5 µM CCh (red) and slow wave activity (SWA, blue). PCI was calculated using Lempel-Ziv compression of the significant MUA (SS(x,t)) contained in a binary matrix. Source: D'Andola et al. (2017). Bistability, causality, and complexity in cortical networks: an in vitro perturbational study. *Cereb Cortex* 91:1–10. Reused with permission. (**C**) Example of decay in sPCI in awake-like state of a cortical slice and during blockade of slow inhibition (CGP 1 µM). (**D**) Example of decay in sPCI reduction in slow oscillatory activity in a cortical slice and during blockade of slow inhibition (CGP 1 µM) Binary matrix SS(x,t) of MUA significantly higher than a threshold activity.

Complexity Index (PCI) is one such method, which determines brain complexity based on the ability of the network to integrate and differentiate the responses and cortical interaction following a particular perturbation (i.e., electrical stimulation) (Casali et al., 2013). Casali et al. (2013) measured brain complexity based on the spatiotemporal distribution of significant electroencephalography (EEG) responses following transcranial magnetic stimulation (TMS). They demonstrated that during NREM sleep, TMS induced bimodal stereotypical EEG responses (Figure 1A), while during wakefulness, TMS triggered complex heterogeneous EEG responses (Figure 1A) (Casali et al., 2013).

The measurement of complexity using PCI in humans can distinguish different levels of consciousness but does not provide information about the mechanisms involved. To provide a mechanistic approach, D'Andola et al., (2017) adapted the PCI measure to the cerebral cortex *in vitro* and found that the measure was able to distinguish variations in cortical complexity for different simulated "brain states" reached by varying neurotransmitter concentrations. The authors found that network complexity was low during slow wave activity, and increased at induced awake-like states by cholinergic and noradrenergic agonists (Figure 5B) (D'Andola et al., 2017). Indeed, it was also demonstrated that simply increasing neuronal excitability and firing rates do not imply higher complexity states measured by perturbational methods (D'Andola et al., 2017; Barbero-Castillo et al., 2020). Thus, while network excitability and neuronal firing patterns are key elements for the normal functioning of cortical networks and for the transition between different brain states, there is not a linear relationship between cortical excitability and complexity. For example, blocking of $GABA_A$-Rs can lead into rather high excitability and epileptiform discharges; however, cortical complexity decreases in these cases (Barbero-Castillo et al., 2020). Decreasing inhibition by blocking $GABA_B$-Rs was found to decrease cortical complexity independently from firing, either departing from an awake-like, asynchronous state (Figure 5C) or from a slow wave activity state (Figure 5D) (Barbero-Castillo et al., 2020), in agreement with the idea that the activation of $GABA_B$-Rs brings in dynamical richness and irregularity to the cortical network (Perez-Zabalza et al., 2020).

INDICATED TO MATCH THE OUTLINE

1 Synaptic transmission through metabotropic $GABA_B$ receptors in thalamus and cortex

i Role of $GABA_B$ receptors in synaptic plasticity in the thalamocortical loop

2 $GABA_B$ receptors and emergent rhythmic patterns: thalamic activity

3 $GABA_B$ receptors and emergent rhythmic patterns: cortical activity

i Mechanisms of termination of Up states

ii $GABA_B$ modulation of cortical complexity

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