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Serotonergic Modulation of the Prefrontal Cortex: From Neurons to Brain Waves

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1. Introduction

Humans are remarkably proficient at some sophisticated and abstract tasks such as learning, memory and flexibility. These tasks depend on the prefrontal cortex, the cortical region most evolved in primates (Fuster, 2001; Miller & Cohen, 2001). The prefrontal cortex includes the most anterior structures of the frontal lobes, with some imprecise anatomical boundaries between different species of mammals. It has been defined across species according to its reciprocal anatomical connections with the mediodorsal nucleus of the thalamus (nucleus MD). The prefrontal cortex controls the activity of many subcortical structures via the excitatory axons of pyramidal neurons. These projection neurons forward the output signals of a complex cortical microcircuit composed of distinct types of excitatory pyramidal neurons and numerous types of inhibitory interneurons. It receives, along with the thalamus, dense innervation from many brain regions, including the serotonergic nuclei of the brainstem. During the last decade, research conducted by many laboratories has revealed that serotonin is a major modulator of prefrontal functions at the behavioral, neuronal and network levels. Its influences on cortical processing are implemented through multiple receptors expressed by pyramidal neurons as well as interneurons. These complex modulatory signals are altered in many psychiatric disorders such as schizophrenia and depression, where changes in receptor expression, neuron activity and brain waves have been observed. Furthermore, many psychiatric treatments -for instance, some antipsychotics and antidepressants- target the serotonergic system and the prefrontal cortex. Thus, understanding the role of serotonergic neurotransmission in prefrontal cortex function is of major importance. Here we present a summary of our findings on the anatomy, neurophysiology and pharmacology of the serotonergic system in the medial prefrontal cortex of the rat.

2. Serotonergic control of prefrontal cortex function

The involvement of serotonin in higher-order cognition is still poorly understood. Research conducted in non-human primates and rodents suggests that serotonin in the prefrontal cortex plays a modulatory role in spatial working memory (Williams et al., 2002) and is critical for cognitive flexibility, its depletion resulting in perseverative behaviours (Clarke et

al., 2004, 2005; Dalley et al., 2011; Robbins, 2000, 2005; Rygula et al., 2010). In addition, serotonin is relevant for behavioral inhibition, since elevated or reduced prefrontal serotonin is followed by deficits in impulse control (Dalley et al., 2002; Passetti et al., 2003; Talpos et al., 2005; Winstanley et al., 2003). Recent studies have provided some insights on the serotonergic receptors implicated in the regulation of cognitive flexibility and response inhibition (Boulougouris et al., 2008; Winstanley et al., 2003, 2004). Deficits in working memory, flexibility and control are associated with various psychiatric disorders, most notably schizophrenia, obsessive-compulsive disorder (OCD) and drug addiction. Thus, further work is required to investigate the specific roles of serotonergic receptors in these cognitive tasks.

The anatomy and neurophysiology of the serotonergic system, however, have been described in much more detail. The interconnections between the raphe nuclei, source of serotonergic neurons, and the distinct aspects of the prefrontal cortex in the rat brain are well known. Anatomical evidence indicates that medial prefrontal cortex neurons project densely to both the dorsal and median raphe nuclei of the brainstem. Conversely, serotonergic neurons of these nuclei send axons to the prefrontal cortex, where serotonin exerts its actions through several receptors expressed by a large population of neurons. These receptors are powerful modulators of cortical activity, both at a single neuron and network levels. In the following sections we describe the anatomy and neurophysiology of the serotonergic system in the rat prefrontal cortex.

2.1 Reciprocal connections between the raphe nuclei and the prefrontal cortex

Dense reciprocal connections exist between the dorsal and median raphe nuclei and the different regions of the medial prefrontal cortex: the cingulate, prelimbic and infralimbic cortices (Groenewegen & Uylings, 2000). Early anatomical studies utilizing retrograde and anterograde tracing methods revealed that all these cortices project to the raphe nuclei (Hajos et al., 1998; Peyron et al., 1998; Sesack et al., 1989). More recently, Vertes (2004) has reported that the prelimbic cortex sends denser axon bundles to the raphe nuclei than the infralimbic cortex. In turn, serotonergic neurons send ramified axons to many cortical areas, including the prefrontal cortex (Groenewegen & Uylings, 2000). This diffuse anatomy allows serotonergic neurons to modulate large cortical regions simultaneously.

The prefrontal-raphe descending pathway and the raphe-prefrontal ascending pathway have been functionally characterized *in vivo* in the anesthetized rat. Raphe projecting neurons in the prefrontal cortex were identified by stimulating electrically their terminals in the raphe nuclei and recording the action potential generated in the soma by the electrical wave travelling backwards along the axon, a phenomenon called antidromic activation (Amargos-Bosch et al., 2004; Celada et al., 2001; Puig et al., 2003, 2005, 2008). Similarly, serotonergic neurons were identified by antidromic activation from the prefrontal cortex (Celada et al., 2001). These approaches have yielded important insights into the relative conduction velocities of glutamatergic and serotonergic axons. The electrical stimulation of the prefrontal cortex was also used to investigate how prefrontal neurons control the activity of serotonergic neurons. A series of *in vivo* experiments indicate that serotonergic neurons in the dorsal raphe nucleus are strongly regulated by prefrontal afferents through a complex cellular mechanism. Prefrontal stimulation mainly inhibits serotonergic activity despite the descending projections are excitatory. This inconsistency may be explained by the presence of 5-HT1A autoreceptors on serotonergic

neurons: a small population of neurons is initially activated by direct excitatory inputs from the prefrontal cortex; this increases the release of serotonin within the dorsal raphe nucleus, which immediately reduces spiking of nearby neurons via 5-HT1A inhibitory autoreceptors. Another mechanism would involve direct excitation of inhibitory interneurons in the dorsal raphe nucleus by prefrontal afferents (Celada et al., 2001; Hajos et al., 1998).

2.2 Expression of serotonergic receptors in prefrontal cortex

The prefrontal cortex consists of a remarkably complex microcircuit composed of numerous types of pyramidal neurons and interneurons. According to Swanson (1998), the rat medial prefrontal cortex is composed of 5 layers. Layer 1 is the most superficial and contains the bodies of inhibitory interneurons and dendrites of pyramidal neurons. Layers 2 and 3 are full of somas of small pyramidal neurons and distinct types of interneurons, whereas layers 5 and 6 are packed with large pyramidal neurons -output neurons whose axons project to subcortical structures- and a myriad of different interneurons. Several classifications of GABAergic interneurons have been made based on their morphology, chemical neuroanatomy and electrophysiological properties (Gupta et al., 2000; Kawaguchi & Kubota, 1997, 1998; Markram et al., 2004; Uematsu et al., 2008).

Over the last 20 years, many efforts have been made to understand the expression pattern of serotonergic receptors in the heterogeneous neuron types present in the prefrontal cortex. Yet, we are still puzzled by the fact that many prefrontal neurons express at least one type of serotonergic receptor and oftentimes co-express several, despite these receptors may exert opposite effects on neuronal activity. For instance, 60% of pyramidal neurons in the rat prefrontal cortex express serotonin receptors 5-HT1A or 5-HT2A, particularly in layer 5 (De Almeida & Mengod, 2007; Kia et al., 1996; Lopez-Gimenez et al., 1997; Martin-Ruiz et al., 2001; Pazos & Palacios, 1985; Pompeiano et al., 1992, 1994; Santana et al., 2004; Weber & Andrade, 2010; Willins et al., 1997). Interestingly, around 80% of these co-express both receptors (Amargos-Bosch et al., 2004; Puig et al., 2010; Santana et al., 2004), although 5-HT1A receptors reduce whereas 5-HT2A receptors increase neuronal spiking (see below). The purpose of this co-expression has yet to be elucidated. However, the distribution of these receptors in different compartments of the pyramidal cell points to a specific role in action potential generation. 5-HT1A receptors are densely located on the axon initial segment (De Felipe et al., 2001), where they may downregulate the generation of action potentials; by contrast, 5-HT2A receptors are abundant on the apical dendrites (Jakab & Goldman-Rakic, 1998; Martin-Ruiz et al., 2001), where they increase excitatory currents (Marek & Aghajanian, 1999) (Figure 1). We have recently found that pyramidal neurons also express 5-HT2C receptors, but the degree of co-expression with 5-HT1A and 5-HT2A receptors is still unknown (Puig et al., 2010).

Cortical GABAergic interneurons are also innervated by serotonergic afferents from the raphe nuclei, as assessed by electron microscopy (De Felipe et al., 1991; Smiley & Goldman-Rakic, 1996). Consistently, populations of neocortical interneurons express serotonin receptors, in particular 5-HT1A, 5-HT2A and 5-HT3A receptors (De Almeida & Mengod, 2007; Jakab and Goldman-Rakic, 2000; Jansson et al., 2001; Morales & Bloom, 1997; Puig et al., 2004, 2010; Santana et al., 2004; Vucurovic et al., 2010; Weber & Andrade, 2010; Willins et al., 1997) (Figure 1). *In situ* hybridization histochemistry has revealed that, unlike pyramidal

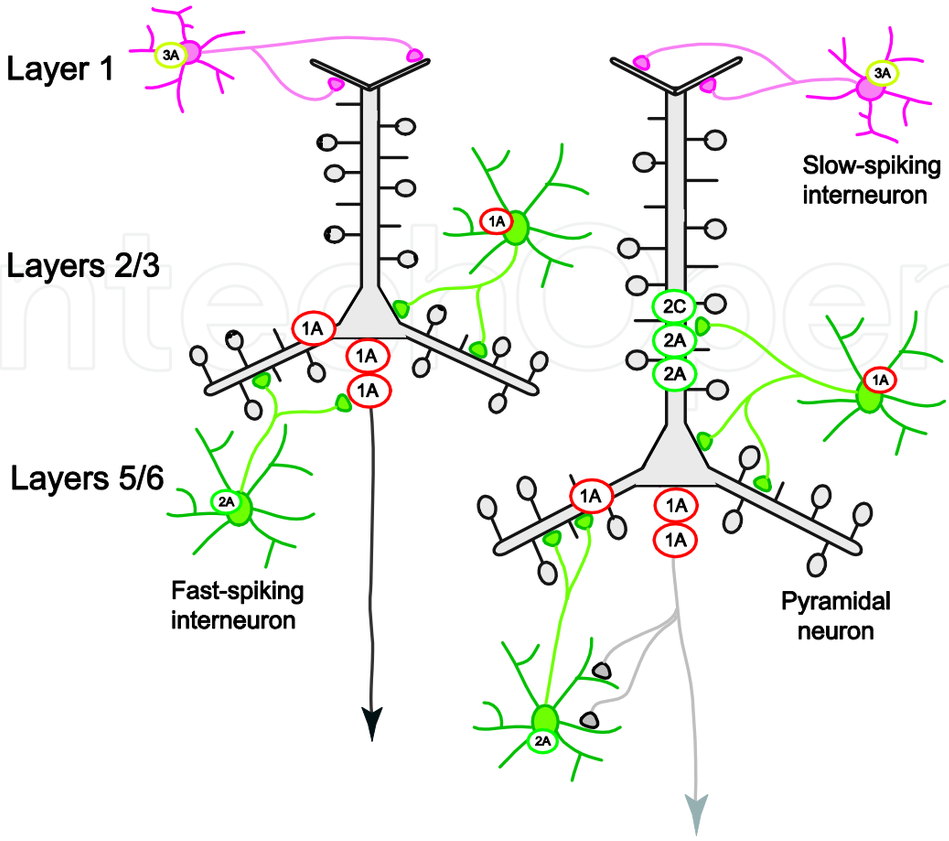

Fig. 1. Localization of serotonin receptors within the prefrontal cortex microcircuit. Many pyramidal neurons in deep layers co-express 5-HT1A and 5-HT2A receptors. In addition, distinct populations of local inhibitory interneurons that express serotonin receptors innervate different compartments of the pyramidal cell: 5-HT1A- and 5-HT2A-expressing fast-spiking interneurons are preferentially located in deep layers where they contact pyramidal neurons at the soma and proximal dendrites; slow-spiking interneurons that express 5-HT3A receptors are located in superficial layers where they innervate pyramidal neurons at the distal dendrites. Modified from Puig et al., 2008.

neurons, two separate populations of fast-spiking interneurons express 5-HT1A and 5-HT2A receptors and not 5-HT2C receptors. These interneurons are more abundant in layers 2, 3 and 5, particularly in layer 5, where each receptor subtype is expressed by 50% of interneurons (Puig et al., 2010). Thus, fast-spiking inhibitory neurons that express 5-HT1A or 5-HT2A mRNAs are enriched in layer 5, just as pyramidal neurons. In addition, a population of slow-spiking interneurons expresses 5-HT3A receptors (Ferezou et al., 2002; Morales et al., 1996; Morales & Bloom, 1997; Puig et al., 2004). These neurons are particularly abundant in layer 1, an area devoid of pyramidal cell bodies but full of their dendrites, where 40% of inhibitory cells express 5-HT3A receptors. In the rat, these neurons also express cholecystokinin (CCK), vasoactive intestinal peptide (VIP) or neuropeptide Y (Ferezou et al., 2002; Vucurovic et al., 2010), whereas 5-HT3 receptors have been localized to calbindin- and calretinin-containing small size interneurons in the monkey (Jakab & Goldman-Rakic, 2000). Therefore, the distribution of 5-HT3A-expressing interneurons is complementary to that of 5-HT1A- and 5-HT2A-expressing interneurons, through which

serotonin can control the entire pyramidal cell (Figure 1). This sophisticated expression pattern of serotonergic receptors in pyramidal neurons and interneurons allows serotonin to exert a profound control over the activity of prefrontal cortex microcircuits.

2.3 Serotonin modulates neuronal activity in prefrontal cortex

With the exception of the 5-HT3 receptors (ligand-gated ion channels), serotonin receptors couple to G-proteins to exert their effects (Hoyer et al., 1994). In the slice preparation, 5-HT1A and 5-HT2A receptors mediate inhibitory and excitatory responses, respectively, in layer 5 pyramidal neurons (Aghajanian & Marek, 1997; Araneda & Andrade, 1991; Arvanov et al., 1999; Marek & Aghajanian, 1998; Tanaka & North, 1993; Zhou & Hablitz, 1999). 5-HT1A hyperpolarizations involve coupling to G_i/G_o proteins and increase in potassium conductance (Gk). 5-HT2A-mediated depolarizations follow activation of G_q/G_{11} proteins and decrease in Gk conductance. Similarly, serotonin hyperpolarizes and depolarizes neocortical interneurons *in vitro* via 5-HT1A and 5-HT2A receptors (Foehring et al., 2002; Jakab & Goldman-Rakic, 1998; Xiang & Prince, 2003; but see Gulledge et al., 2007), and induces fast membrane potential depolarizations via 5-HT3A receptors (Ferezou et al., 2002; Foehring et al., 2002; Xiang & Prince, 2003).

To investigate the roles of these receptors *in vivo* we stimulated electrically the raphe nuclei – which induces measurable increases of prefrontal serotonin release (Gartside et al., 2000; McQuade & Sharp, 1995) - while recording the responses on identified pyramidal neurons and interneurons of the prefrontal cortex in anesthetized rats. Serotonin evoked three different responses on pyramidal neurons: inhibitions (66%), excitations (13%) and biphasic responses (20%), composed of an initial inhibition followed by an excitation (Puig et al., 2005) (Figure 2). Considering the proportion of inhibitions and mixed responses, serotonin exerts preferential inhibitory actions on the prefrontal cortex *in vivo*, similar to those observed in early microiontophoretic and stimulation studies (Ashby et al., 1994; Jacobs & Azmitia, 1992; Mantz et al., 1990). Pharmacological manipulations confirmed that the decreases and increases of activity were mediated by 5-HT1A and 5-HT2A receptors, respectively, and that the biphasic responses likely corresponded to pyramidal neurons co-expressing both receptors (Amargos-Bosch et al., 2004; Hajos et al., 2003; Puig et al., 2003, 2005). In addition, the administration of the 5-HT2A/2C receptor agonist DOI increased activity of pyramidal cells, an effect reversed in most neurons by a selective 5-HT2A receptor antagonist (Martin-Ruiz et al., 2001; Puig et al., 2003). However, in a small population of neurons the 5-HT2A receptor antagonist failed to reverse DOI's induced excitation. This suggests that 5-HT2C receptors also mediate excitatory responses *in vivo* in a subpopulation of pyramidal neurons, in accordance with their pattern of expression in the prefrontal cortex (Puig et al., 2010).

Noteworthy, the amount of biphasic responses (20%) recorded was smaller than the reported proportion of pyramidal neurons co-expressing 5-HT1A and 5-HT2A receptors (45-50%). So, possibly many pyramidal neurons that co-express these receptors are indeed inhibited by serotonin. A plausible explanation would involve the dense localization of 5-HT1A receptors on the axon initial segment of pyramidal cells (Azmitia et al., 1996; Cruz et al., 2004; Czyrak et al., 2003; De Felipe et al., 2001; Martin-Ruiz et al., 2001), coincident with the cortical GABAergic axo-axonic synapses between chandelier cells and pyramidal cells (De Felipe et al., 2001; Somogyi et al., 1998), and downstream of 5-HT2A receptors in the process of spike generation (Figure 1). This would assign a prominent inhibitory role to 5-HT1A receptors in the control of pyramidal activity.

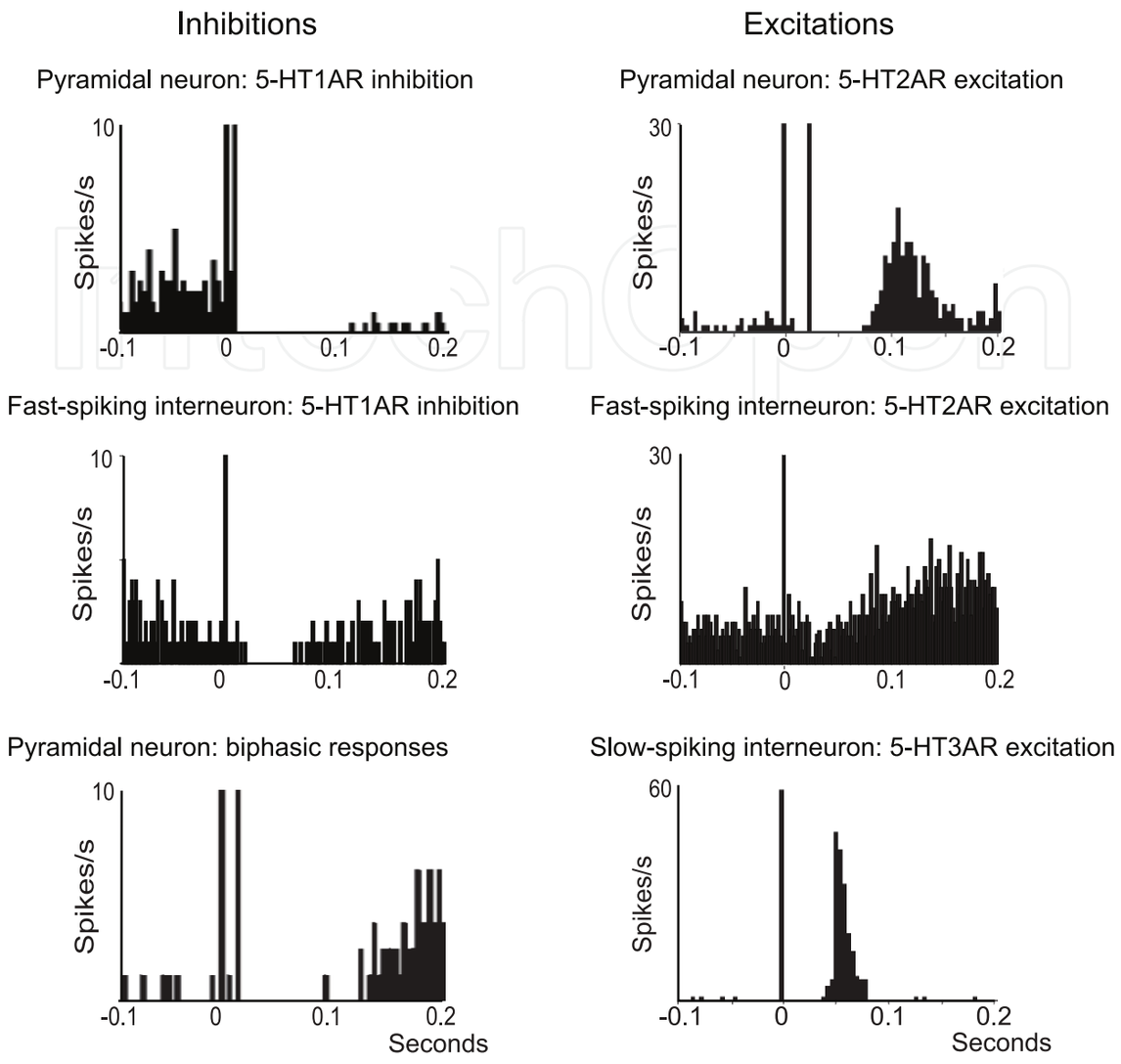

Fig. 2. Serotonin inhibits and activates distinct populations of prefrontal neurons. Peri-stimulus histograms depicting the firing rate of pyramidal neurons and different types of interneurons recorded in the prefrontal cortex of anesthetized rats during electrical stimulation of the dorsal raphe nucleus (time 0), which induces release of serotonin in the prefrontal cortex. Note that 5-HT1A-mediated inhibitions are shorter in fast-spiking interneurons compared to pyramidal neurons and that 5-HT3A-mediated excitations have a shorter delay and duration than 5-HT2A-mediated excitations. Modified from Amargos-Bosch et al., 2004 and Puig et al., 2004, 2010.

A second possibility entails an activation of non-serotonergic inhibitory afferents to the prefrontal cortex from the raphe nuclei. GABAergic projection neurons have been found in the dorsal raphe nucleus, and many inhibitions have an initial component independent of 5-HT1A receptors (Li et al., 2001; Puig et al., 2005). Moreover, the involvement of direct GABAergic projections to the prefrontal cortex is suggested by the short-latency (≤ 8 ms) inhibitions recorded in prefrontal pyramidal neurons that cannot be accounted for by the slow conduction velocity of serotonergic axons (Puig et al., 2005).

GABAergic interneurons may play an important role in the inhibitory effects of serotonin as well. We have recently shown that subgroups of prefrontal fast-spiking interneurons are modulated by 5-HT1A and 5-HT2A receptors *in vivo* (Puig et al., 2010). Akin to previous studies, we stimulated electrically the dorsal raphe nucleus and recorded the responses on parvalbumin-expressing fast-spiking interneurons of the prefrontal cortex. Parvalbumin is a calcium binding protein selectively expressed by this type of interneuron (Kawaguchi & Kubota, 1997; Uematsu et al., 2008). We observed 5-HT1A-mediated decreases and 5-HT2A-mediated increases of activity in 61% and 10% of the recorded cells, respectively (Figure 2). However, unlike pyramidal neurons, we found very few biphasic responses (6.5%; Puig et al., 2010). This may be due to the fact that separate populations of fast-spiking interneurons express 5-HT1A and 5-HT2A receptors. Again, a predominance of 5-HT1A-mediated inhibitions indicates that serotonin exerts a potent inhibitory drive on cortical fast-spiking interneurons, similar to that on pyramidal neurons. On a similar pace, we identified slow-spiking interneurons in superficial layers of the prefrontal cortex that are excited by serotonin through 5-HT3A receptors (Puig et al., 2004). Interestingly, the latency and duration of the 5-HT3A-mediated excitations were shorter than those elicited by 5-HT2A receptors in pyramidal and fast-spiking neurons of the same area (Figure 2). This is consistent with this receptor being an ion channel and not coupled to G-proteins. Thus, not only is the expression pattern of 5-HT2A- and 5-HT3A-expressing interneurons complementary, but the timing of their activation by serotonin is finely tuned as well.

2.4 Serotonin modulates brain waves in prefrontal cortex

We have recently uncovered that serotonin is a potent modulator of slow waves in the prefrontal cortex (Puig et al., 2010). Under chloral hydrate anesthesia, the predominant oscillatory activities recorded through intracortical field potentials are slow waves (< 2 Hz) that resemble the slow rhythms of natural slow-wave sleep. Slow waves are thought to be critical for memory consolidation (Ji & Wilson, 2007; Marshall et al., 2006; Landsness et al., 2009; Louie & Wilson, 2001; Stickgold, 2005), and are generated by synchronized neuronal ensembles that oscillate between periods of activity (UP states) and silence (DOWN states). UP and DOWN states reflect alternating periods of membrane depolarization and hyperpolarization of large neuronal networks (Contreras & Steriade, 1995; Mukovski et al., 2007; Steriade et al., 1993).

We stimulated the dorsal raphe nucleus at a frequency similar to the discharge rate of serotonergic neurons (1 Hz) in anesthetized rats. The stimulations consistently and reversibly increased in the frequency of slow waves: UP and DOWN cycles appeared more irregular and of shorter duration and the peak of the power spectra (that marks the predominant frequency) increased significantly from 0.74 to 0.94 Hz (Figure 3). This suggests that the 1 Hz stimulations were imposing their frequency onto the cortical network. In fact, increasing the release of serotonin into the cortex -by augmenting the intensity of the stimulations- reliably imposed a frequency of 1 Hz on slow oscillations. Remarkably, serotonin appeared to evoke this increase in frequency by promoting the initiation of UP states from DOWN states with a very short latency. Therefore, the activity of serotonergic neurons in the raphe nuclei may directly regulate the frequency of cortical slow oscillations by promoting UP states. Moreover, during raphe stimulations the amplitude of slow waves was reduced compared to pre-stimulation epochs, and the time that slow waves spent in UP states was greater than before or immediately after the stimulations (i.e. DOWN state

potentials were reduced; Figure 3B). Since UP states are generated by the synchronous depolarization of large ensembles of cortical neurons, these results suggest that serotonin might have excitatory actions on cortical networks.

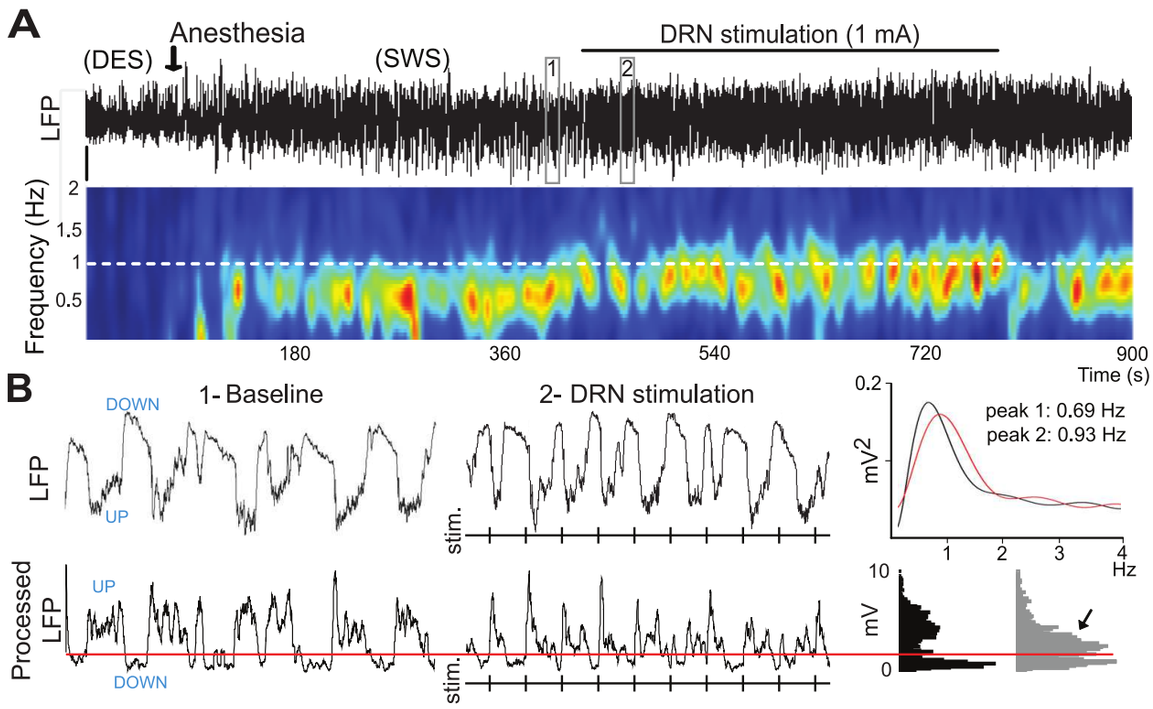

Fig. 3. Serotonin modulates slow waves in prefrontal cortex.
Electrical stimulation of the dorsal raphe nucleus (DRN) at 1 Hz increases the frequency and reduces de amplitude of cortical slow waves (< 1 Hz). (A) Top, local field potential (LFP) signal depicting an epoch of desynchronization (DES, absence of slow waves) and anesthesia-induced slow-wave sleep (SWS) following the injection of chloral hydrate anesthesia. Boxes 1 and 2 are expanded in (B). Bottom, time-frequency representation depicting the change in power (root mean square of the amplitude) over time (red indicates high power, blue low power). White dashed line marks the frequency of stimulation. Note that the predominant band increases in frequency towards the frequency of stimulation during DRN stimulation. (B) Top, expanded 10-second traces from (A). Vertical lines correspond to times of DRN stimulation. Power spectra for 1 min segments that contain the 10 s traces in boxes 1 and 2 are shown on the far right. Bottom, LFPs were processed off-line for an accurate measure of UP state duration. A threshold was set (red line) to discriminate - UP states. Note the increase in UP state potentials during the stimulations (arrow). Modified from Puig et al., 2010.

Indeed, high frequency stimulation of the dorsal raphe nucleus (100 Hz), which induces a massive release of serotonin in the cortex, completely suppressed cortical slow waves by eliminating DOWN states (Puig et al., 2010). These results support the proposed role of the serotonergic system in modulating the transition between sleep and awake states (Dringenberg & Vanderwolf, 1997; Portas et al., 2000). Furthermore, the administration of an antagonist of 5-HT2A/2C receptors altered slow waves, but not antagonists of 5-HT1A or 5-HT2C receptors (Figure 4). This implicates 5-HT2A receptors in the regulation of slow

waves. Blockade of 5-HT2A receptors desynchronized slow oscillations by reducing the number, duration and amplitude of DOWN states, which resulted in a significant increase of UP state potentials similar to that observed after raphe stimulation (Puig et al., 2010).

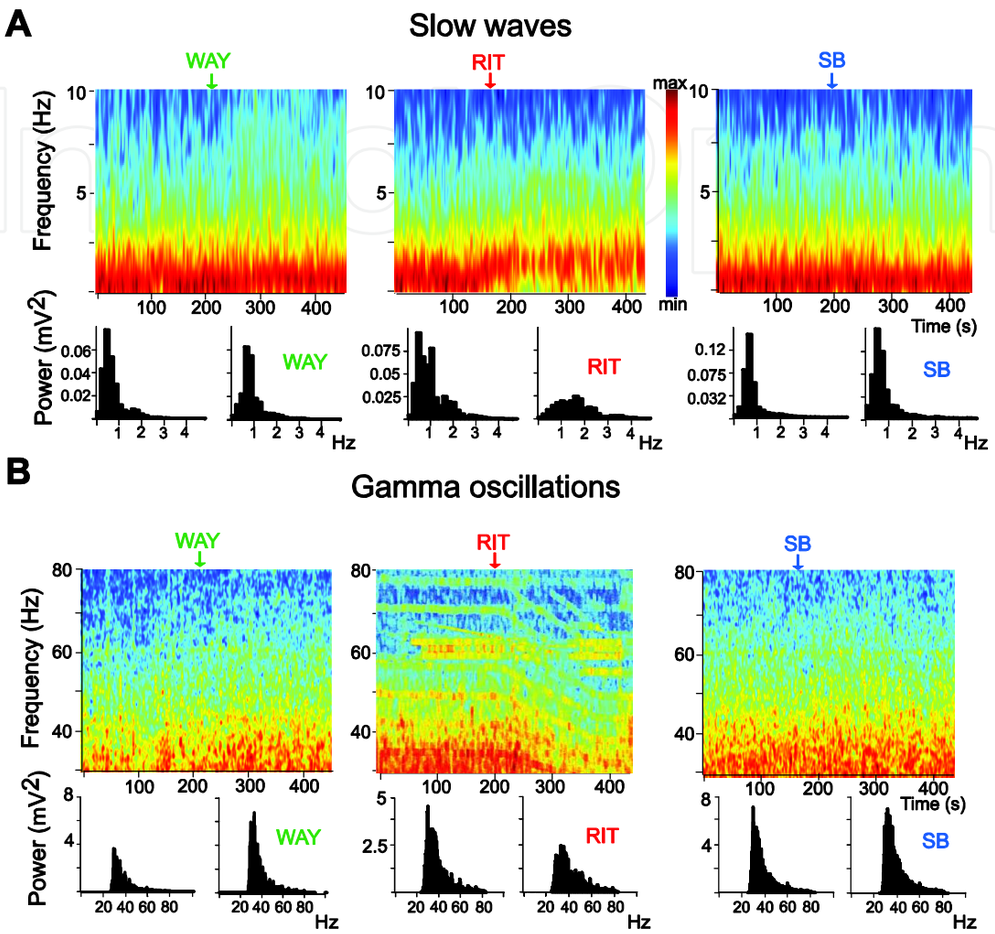

Fig. 4. Serotonin receptors modulate slow and gamma oscillations in prefrontal cortex. Effect of WAY (WAY100635, 5-HT1A receptor antagonist), RIT (ritanserin, 5-HT2A/2C receptor antagonist) and SB (SB242084, 5-HT2C receptor antagonist) on the power of slow waves and gamma oscillations in the rat prefrontal cortex. (A) The power of slow waves decreases after injection of RIT but not SB or WAY, indicating a modulation by 5-HT2A receptors. (B) WAY increases whereas RIT decreases the power of gamma oscillations. This suggests that serotonin regulates gamma rhythms both via 5-HT1A and 5-HT2A receptors. Modified from Puig et al., 2010.

In addition, serotonin exerts a strong modulation of prefrontal gamma oscillations (30-80 Hz). Gamma rhythms provide a temporal structure for cognitive tasks such as attention, sensory processing and working memory (Howard et al., 2003; Singer, 1999; Ward, 2003). We found that blockade of 5-HT1A receptors increases whereas blockade of 5-H2A receptors decreases the amplitude of gamma waves (Figure 4; Puig et al., 2010). Since networks of fast-spiking interneurons generate and are modulated by gamma oscillations (Bartos et al., 2007; Cardin et al., 2009; Puig et al., 2008; Whittington & Traub, 2003), we

hypothesize that serotonin regulates gamma rhythms through fast-spiking interneurons expressing 5-HT1A and 5-HT2A receptors. There are a number of observations that support this. First, high-frequency stimulation of the dorsal raphe nucleus reduces the amplitude of gamma waves in the prefrontal cortex and, as mentioned earlier, serotonin predominantly inhibits cortical fast-spiking interneurons. Second, blockade of 5-HT1A receptors increases the amplitude of gamma waves and the spiking of 5-HT1A-expressing fast-spiking interneurons, while sharpening the synchronization of these neurons to gamma cycles. Thus, stimulation of cortical 5-HT1A receptors would desynchronize gamma oscillations by reducing the activity and synchronization of 5-HT1A-expressing fast-spiking interneurons. Third, blockade of 5-HT2A receptors decreases the amplitude of gamma waves and desynchronizes 5-HT2A-expressing fast-spiking interneurons from gamma waves. Hence, stimulation of cortical 5-HT2A receptors would enhance gamma oscillations by synchronizing 5-HT2A-expressing fast-spiking interneurons. Fourth, fast-spiking interneurons in the prefrontal cortex do not express 5-HT2C receptors and, consistently, blockade of these receptors does not alter gamma oscillations. Finally, the interplay between pyramidal neurons and fast-spiking interneurons further enhances gamma oscillations. Thus, during anesthesia-induced sleep-like states serotonin may down regulate gamma oscillations simply because it inhibits most pyramidal and fast-spiking neurons.

2.5 Dual actions of serotonin on prefrontal cortex networks

The data presented above suggest that serotonin modulates neuron activity and network oscillations in the prefrontal cortex in remarkably different ways, at least during anesthesia-induced slow-wave sleep. It decreases spiking of a large population of neurons while exciting their membranes so that there is a switch from DOWN-hyperpolarizing to UP-depolarizing states during slow waves. How can these two opposing effects be reconciled? Serotonin may be acting upon 5-HT1A receptors on the soma and axon initial segment of pyramidal neurons to prevent generation of action potentials while promoting the increase of excitatory postsynaptic potentials (EPSCs) on their apical dendrites via 5-HT2A -and perhaps 5-HT2C- receptors. Oscillatory activities are recorded through local field signals that reflect the summation of postsynaptic potentials in dendrites, and recent studies suggest that they are independent of action potential generation. By contrast, spiking activity represents the results of local processing (Monosov et al., 2008; Nielsen et al., 2006). We propose that serotonin plays a dual action on cortical pyramidal networks by enhancing synaptic inputs onto the dendrites while down-regulating spiking at the axon level.

It is well documented that some interneurons are potent modulators of pyramidal membrane potentials and that they can innervate many pyramidal neurons simultaneously. Thus, it is fair to assume that interneurons may participate in the generation of UP and DOWN states by inhibiting large populations of pyramidal cells synchronously. Nevertheless, a role for inhibitory interneurons in the proposed dual model of serotonin actions is unclear. First, superficial layers of the cortex -that are rich in pyramidal dendrites- contain 5-HT3A-expressing interneurons, whose activation by serotonin should indeed decrease excitability of distal pyramidal dendrites. Second, it is unknown at this time what compartments of the pyramidal cell 5-HT1A- and 5-HT2A-expressing fast-spiking interneurons interact with. In a configuration consonant with our model, 5-HT2A-containing interneurons would preferentially innervate the soma and axon of pyramidal

neurons, whereas 5-HT1A-containing interneurons would do so on pyramidal dendrites (Figure 1). Clearly, further work is needed to elucidate the exact role of serotonin-modulated interneurons on the cortical microcircuit.

The proposed dual model described earlier is based on observations obtained during anesthesia-induced slow-wave sleep states. Although it has been reported a participation of serotonin in the transition between sleep and alertness, it is currently poorly understood how serotonin differentially modulates prefrontal microcircuits during distinct arousal states. In that sense, some of our recent work has shed some light into this issue (Puig et al., 2008, 2010). We recorded fast-spiking interneurons *in vivo* in the rat prefrontal cortex under chloral hydrate anesthesia. By adjusting the level of anesthesia we allowed short-lasting epochs of cortical desynchronization, periods of time with absence of slow waves that resemble awake states. This manipulation allowed us the examine the firing patterns of cortical neurons during sleep-like states (deep anesthesia) and wake-like states (light anesthesia). We identified two populations of fast-spiking interneurons based on the activity during cortical UP states and the difference in spiking between sleep-like and wake-like states. One population preferentially discharges during the first half of UP states ('early' cells) and decreases spiking during wake-like states. A second population behaves in the opposite manner: it predominantly fires on the second half of UP states ('late' cells) and increases dramatically the activity during wake-like states. This suggests that this latter population may be responsible for generating the gamma oscillations associated with cognitive processing during wakefulness. Intriguingly, these two populations of interneurons are coupled to different phases of gamma cycles, suggesting a sequence of activation from 'early' to 'late' neurons (Puig et al., 2008). Altogether, subpopulations of cortical interneurons may play different but complementary roles during sleep and alertness. We assessed the effects of serotonin on these two neuronal populations during sleep-like and wake-like scenarios (Puig et al., 2010). Although serotonin inhibited most fast-spiking neurons during both states, there was a remarkable increase in the proportion of excited cells during wake-like states. Consistently, the 'late' population (which is more active during alertness) showed a greater amount of excitations. Thus, serotonin may activate a larger population of cortical interneurons during alertness, exerting a more balanced inhibition and excitation which could provide a fine control of gamma oscillations during cognitive tasks.

3. Relevance for psychiatric disorders

Prefrontal function and metabolism is altered in patients with severe psychiatric disorders (Andreasen et al., 1997; Drevets, 2001; Weinberger et al., 1994). For instance, cognitive deficits in schizophrenia patients are mediated by derangements in brain circuits involving the prefrontal cortex (Bertolino et al., 2000; Elvevag & Goldberg, 2000), and an imbalance in glucose metabolism between prefrontal cortex and several anatomically related areas has been described (Andreasen et al., 1997). Similarly, abnormal glucose utilization has been consistently found in prefrontal cortex of patients with major depression (decrease) and post-traumatic stress disorder (increase). Several observations support a role for serotonin receptors in the pathophysiology of these mental illnesses. First, the expression of some serotonin receptors is abnormal in the frontal lobes of psychiatric patients (Arango et al., 1997; Gurevich et al., 2002); and second, hallucinogens such as LSD or DOI are 5-HT2A

agonists and atypical antipsychotics are potent 5-HT2A antagonists (Artigas, 2010; Kroeze & Roth, 1998; Meltzer, 1999; Meltzer & Huang, 2008).

The effects of the hallucinogen DOI have been examined on the activity of pyramidal neurons in the rat prefrontal cortex. DOI, via stimulation of cortical 5-HT2A receptors, increases and decreases the firing rate of distinct subpopulations of pyramidal neurons (Puig et al., 2003). Increases of activity might follow direct stimulation of 5-HT2A receptors, whereas the decreases likely involve nearby interneurons activated by this receptor. Thus, cortical interneurons expressing 5-HT2A receptors may play a crucial role in the actions of some hallucinogens and antipsychotics. Unfortunately, we are unaware of any study that has examined the *in vivo* effects of specific hallucinogens and antipsychotics on this particular population of interneurons. In our 2010 study (Puig et al., 2010) the effects of the selective 5-HT2A/2C antagonist ritanserin were assessed on a very small group of fast-spiking interneurons, rendering inconclusive results. The results yielded by these investigations would be very relevant considering that altered GABA neurotransmission has been reported in schizophrenia. Transcript levels of GAD65/67, enzymes responsible for most GABA synthesis in the cortex, are consistently lower in the prefrontal cortex of subjects with schizophrenia, especially in fast-spiking interneurons (Gonzalez-Burgos et al., 2010; Lewis et al., 2005, 2011).

It has been described in recent years that many psychiatric patients show altered brain waves in a variety of brain regions (Basar & Güntekin, 2008). For instance, the synchronization of slow (<1 Hz), delta (1-4 Hz) and gamma (30-80 Hz) bands is reduced in schizophrenia, major depression and bipolar disorder (Cho et al., 2006; Hoffmann et al., 2000; Keshavan et al., 1998; Spencer et al., 2003; Uhlhaas & Singer, 2006). Remarkably, the hallucinogen and 5-HT2A receptor agonist DOI reduces the amplitude of low frequency oscillations (slow and delta) in the prefrontal cortex of anesthetized rats (Celada et al., 2008). DOI's effects on cortical networks may derive from a depolarizing action on a large population of 5-HT2A-expressing neurons, consistent with the dual model presented earlier. This effect was reversed by a selective antagonist of 5-HT2A receptors, and by the classical and atypical antipsychotics haloperidol and clozapine. The attenuation of DOI-induced alterations of slow oscillations is possibly related to the ability of these drugs to suppress psychotic symptoms in schizophrenic patients. Interestingly, haloperidol was less effective than clozapine in reversing the effects, which may likely be explained by the higher affinity of the latter for 5-HT2A receptors. Surprisingly, the 5-HT2A/2C antagonist ritanserin reduces the amplitude of slow oscillations via blockade of 5-HT2A receptors as well (Figure 4; Puig et al., 2010). Thus, either pharmacological stimulation or blockade of 5-HT2A receptors with DOI and ritanserin, respectively, desynchronizes slow rhythms in the prefrontal cortex. This strongly suggests that a balanced activation of 5-HT2A receptors is critical for a stable synchronization of slow waves. Interestingly, a reduction in slow wave activity has been detected in patients with schizophrenia during sleep (Hoffmann et al., 2000). We propose that a potential source of this decrease could be an unbalanced stimulation of cortical 5-HT2A receptors. Impaired gamma oscillations and synchrony have been reported in schizophrenia patients as well (Basar & Güntekin, 2008; Cho et al., 2006; Gonzalez-Burgos & Lewis, 2008, 2010; Spencer et al., 2003; Uhlhaas and Singer, 2006). Unfortunately, the effects of DOI and antipsychotics were not assessed on cortical gamma oscillations in the studies described earlier. Detailed knowledge of the brain mechanisms underlying serotonergic modulation of gamma oscillations could provide valuable

information for our understanding of why most schizophrenia treatments are largely ineffective at improving cognition.

4. Conclusions

The prefrontal cortex is a key area for the control of higher-order executive tasks such as learning, working memory, flexibility and behavioral control. The prominent innervation by serotonergic afferents and the dense expression of serotonergic receptors in this region suggest that serotonin is a major modulator of prefrontal cortex function. Over the last decade we and others have unveiled the complex pattern of expression of the most abundant serotonergic receptors in this area, and have described in some detail how these receptors modulate the activity of pyramidal neurons and interneurons *in vivo*. From these series of investigations we can conclude that serotonin primarily inhibits pyramidal and fast-spiking neuronal activity via 5-HT1A receptors and excites a small population of these via 5-HT2A receptors. The exquisite expression pattern of 5-HT1A, 5-HT2A and 5-HT3A receptors in distinct populations of fast-spiking and slow-spiking interneurons allows serotonin to control the different compartments of pyramidal neurons more or less independently. Moreover, serotonin finely tunes the timing of its actions through the different properties of its receptors (G-coupled vs. ion channels) and the cell type that expresses them. This sophisticated mechanism of control might be important for the precise computations required during cognitive tasks.

Serotonin is also a potent modulator of brain waves in the prefrontal cortex. Serotonergic neurons of the raphe nuclei may play a role in regulating the frequency and amplitude of slow oscillations during sleep, a phenomenon critical for memory consolidation. Serotonin exerts an excitatory effect on cortical networks during slow wave sleep via 5-HT2A receptors. Thus, serotonin may play dual actions on large pyramidal ensembles by down regulating spiking while enhancing the inputs onto the dendrites. This is possibly accomplished by 5-HT1A receptors located on the axon initial segment of pyramidal neurons and 5-HT2A receptors located on the apical dendrites. Further studies are required to elucidate the exact involvement of interneurons in this complex modulation. Serotonin regulates the amplitude of gamma waves as well, perhaps through 5-HT1A- and 5-HT2A-expressing fast-spiking interneurons. Interestingly, the latter population tends to be more active during wakefulness whereas the former is active both during sleep and wakefulness. Therefore, serotonin may adjust the activity of these two populations of interneurons to control the amplitude of gamma waves during executive tasks.

The prefrontal cortex is altered in many mental illnesses and some psychiatric treatments target serotonergic receptors in this area. At this time, more work is needed to really comprehend the alterations of the serotonergic system in these disorders. In fact, the role of serotonin in the prefrontal cortex of the healthy brain is still poorly understood. Recent studies have revealed that GABAergic neurotransmission in interneurons may be altered in some of these mental conditions. The fact that interneurons in the prefrontal cortex express serotonergic receptors and most likely play a critical role in modulating cortical activity and brain waves makes them good candidates as targets for future psychiatric treatments.

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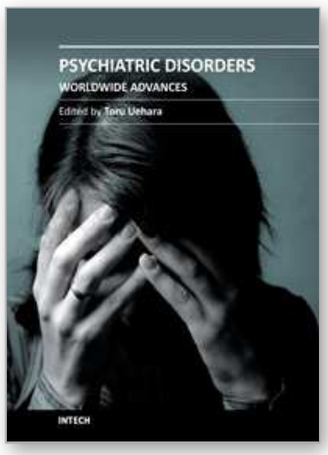

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A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the filed. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in â€œworld psychiatryâ€.

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