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DOI

[10.3389/fnsyn.2017.00002](https://doi.org/10.3389/fnsyn.2017.00002)

Publication date

2017

Document Version

Final published version

Published in

Frontiers in Synaptic Neuroscience

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Citation for published version (APA):

Meunier, C. N. J., Chameau, P., & Fossier, P. M. (2017). Modulation of synaptic plasticity in the cortex needs to understand all the players. *Frontiers in Synaptic Neuroscience*, 9, [2]. <https://doi.org/10.3389/fnsyn.2017.00002>

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Modulation of Synaptic Plasticity in the Cortex Needs to Understand All the Players

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The prefrontal cortex (PFC) is involved in cognitive tasks such as working memory, decision making, risk assessment and regulation of attention. These functions performed by the PFC are supposed to rely on rhythmic electrical activity generated by neuronal network oscillations determined by a precise balance between excitation and inhibition balance (E/I balance) resulting from the coordinated activities of recurrent excitation and feedback and feedforward inhibition. Functional alterations in PFC functions have been associated with cognitive deficits in several pathologies such as major depression, anxiety and schizophrenia. These pathological situations are correlated with alterations of different neurotransmitter systems (i.e., serotonin (5-HT), dopamine (DA), acetylcholine...) that result in alterations of the E/I balance. The aim of this review article is to cover the basic aspects of the regulation of the E/I balance as well as to highlight the importance of the complementarity role of several neurotransmitters in the modulation of the plasticity of excitatory and inhibitory synapses. We illustrate our purpose by recent findings that demonstrate that 5-HT and DA cooperate to regulate the plasticity of excitatory and inhibitory synapses targeting layer 5 pyramidal neurons (L5PyNs) of the PFC and to fine tune the E/I balance. Using a method based on the decomposition of the synaptic conductance into its excitatory and inhibitory components, we show that concomitant activation of D1-like receptors (D1Rs) and 5-HT_{1A}Rs, through a modulation of NMDA receptors, favors long term potentiation (LTP) of both excitation and inhibition and consequently does not modify the E/I balance. We also demonstrate that activation of D2-receptors requires functional 5-HT_{1A}Rs to shift the E-I balance towards more inhibition and to favor long term depression (LTD) of excitatory synapses through the activation of glycogen synthase kinase 3 β (GSK3 β). This cooperation between different neurotransmitters is particularly relevant in view of pathological situations in which alterations of one neurotransmitter system will also have consequences on the regulation of synaptic efficacy by other neurotransmitters. This opens up new perspectives in the development of therapeutic strategies for the pharmacological treatment of neuronal disorders.

OPEN ACCESS

Edited by:

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Received: 25 October 2016

Accepted: 13 January 2017

Published: 01 February 2017

Citation:

Meunier CNJ, Chameau P and Fossier PM (2017) Modulation of Synaptic Plasticity in the Cortex Needs to Understand All the Players. *Front. Synaptic Neurosci.* 9:2. doi: 10.3389/fnsyn.2017.00002

Keywords: prefrontal cortex, serotonin, dopamine, LTP and LTD, neuromodulation

INTRODUCTION

The prefrontal cortex (PFC) plays an important role in the processing of cognitive functions such as attention, memory, decision making and more specifically in working memory (Fuster, 2001; Miller and Cohen, 2001). Its ability to integrate and process sensory information is ensured by a neuronal network receiving numerous afferent connections from sensory areas and making efferent connections to motor area and subcortical area (Miller and Cohen, 2001; Uylings et al., 2003). The higher-order brain functions performed by the PFC are supposed to rely on rhythmic electrical activity generated by neuronal network oscillations. Indeed, cortical networks are permanently active and their activity patterns, depending on the wakefulness or sleep states, are characterized by slow oscillations of the neuronal membrane potential (so-called up and down states) during slow wave sleep and by fluctuations around a depolarized level (persistent up state) during REM sleep and wakefulness (Steriade et al., 2001). Membrane potential fluctuations, the above described phase transitions between up and down state, can be spontaneously generated by local (surrounding) cortical synaptic connections. The up state is initiated by the recruitment of neurons through recurrent excitation and is regulated by local feedback inhibition, pyramidal and non-pyramidal neurons receiving strong barrages of synaptic input that cause membrane depolarization and action potential firing (up state). The down state is characterized by neuronal hyperpolarization, a reduction in synaptic bombardment and a reduction of action potential activity (Sanchez-Vives and McCormick, 2000; Timofeev et al., 2000; Compte et al., 2003; Shu et al., 2003a). This transition to the down state may result from synaptic depression or the buildup of intracellular calcium and sodium concentrations that activate potassium channels in neurons of the local network (Contreras et al., 1996; Sanchez-Vives and McCormick, 2000; Timofeev et al., 2000). These cortical network rhythms are determined by a precise balance between excitation and inhibition that results from the coordinated activities of recurrent excitation and feedback and feedforward inhibition (Shu et al., 2003b; Haider et al., 2006). The initiation of the up state is characterized by an increase in excitatory conductance followed by an increase in inhibitory conductance. Following onset and during the up state, excitatory and inhibitory conductances remain proportionally increased and dynamically balanced (Haider et al., 2006). This balanced activity keeps neurons at a noisy and elevated level of depolarization near firing threshold and prevents aberrant network activity. In addition to being spontaneously generated (Sanchez-Vives and McCormick, 2000; Timofeev et al., 2000; Shu et al., 2003b), both transitions from up to down and from down to up can be triggered by sensory input and activation of afferent inputs (Anderson et al., 2000; Petersen et al., 2003; Shu et al., 2003a; MacLean et al., 2005; Rigas and Castro-Alamancos, 2007).

Within cortical networks, interneurons are in charge of the dynamic adjustment of the level of excitation, and their role in the maintenance of a dynamic balance between excitation and inhibition balance (E-I balance) is essential in cortical function (Shu et al., 2003b). The E-I balance is a value that

reflects the activity of neuronal network at one time (Haider and McCormick, 2009). A proper E-I balance is essential for physiological processes such as sensory perception, short term memory, long term memory and development (Saghatelyan et al., 2001; Egorov et al., 2002; Monier et al., 2003; Zhang et al., 2011). Alterations in maintaining the E-I balance have been observed in several pathologies such as epilepsy and autism. For instance, an increase in GABAergic transmission leading to a change in excitation has been observed in epileptic tissue (Cossart et al., 2001). In the case of autism, the E-I balance appears to vary in the direction of greater excitation (Rubenstein and Merzenich, 2003; Powell, 2004). These pathologies, currently considered as polygenic and multifactorial disorders, are characterized by a disruption of normal cortical connections with aberrant synaptic function and disorganized neurotransmitter interactions (Stephan et al., 2009). For instance, dysfunctions of dopaminergic, glutamatergic and serotonergic systems have been associated with the pathophysiology of schizophrenia and major depression (Marek, 2007; Kantrowitz and Javitt, 2012). Although the pathophysiology of schizophrenia has been associated with alterations of the dopaminergic system (Creese et al., 1976; Meisenzahl et al., 2008), others suggest that the use of antipsychotic drugs acting at both the serotonergic and dopamine (DA) systems must be considered (Meltzer et al., 2004; Newman-Tancredi et al., 2007; Jones and McCreary, 2008; Newman-Tancredi, 2010; Meltzer and Massey, 2011; Newman-Tancredi and Kleven, 2011). Several studies have suggested that an imbalance between DA and serotonin (5-HT) systems could be the cause of adverse side effects observed during treatment of some pathologies (Borah and Mohanakumar, 2007; Carta et al., 2007; Navailles et al., 2010). These observations offer the possibility of a new therapeutic approach which consists in combining drugs that target several receptors to neuromodulators in the treatment of schizophrenia and major depression in order to reassess a proper E-I balance required for harmonious brain functions.

Synaptic plasticity is a fundamental property of the brain which allows the nervous system to adapt its response to experience. In this review article, we first briefly address the general mechanisms of synaptic plasticity leading to long term potentiation (LTP) or Depression of excitatory and inhibitory synapses and we introduce the notion of E-I balance. We also illustrate how the method we developed to determine the E-I balance offers the possibility to study simultaneously the plasticity of excitatory and inhibitory inputs on a layer 5 pyramidal neuron (L5PyN). The second part of this review article highlights our recent findings regarding the cooperation between serotonergic and dopaminergic systems within the PFC in the orientation of synaptic plasticity towards potentiation or depression.

HOW TO LEARN: SYNAPTIC PLASTICITY

Synaptic plasticity is a fundamental property of neuronal circuits which endows the nervous system the ability to adapt its responses to a changing environment (sensory information). It confers the brain the capacity to adapt its behavior and to

anticipate and control executive functions (Feldman, 2009). First postulated by Hebb (1949), the concept of synaptic plasticity was substantiated by Bliss and Lomo (1973) who demonstrated that, in hippocampus, a high frequency stimulation (HFS) of excitatory synapses induced a persistent enhancement of excitatory neurotransmission, the so called LTP. This extensively studied synaptic property is supposed to be the basic mechanism of learning and memory. It is initiated within a short period of time (a few seconds), it is stable and persistent after induction (for several weeks *in vivo*), it is initiated by frequencies of stimulation (theta burst) similar to the neuronal rhythmic activity observed in cortical networks engaged in various information processing tasks. Long term depression (LTD), the opposite of LTP, corresponds to a long-lasting decrease of synaptic efficacy (several hours) in response to low frequency stimulations (Dudek and Bear, 1992; Bear and Malenka, 1994).

These two forms of long-lasting synaptic plasticity do not oppose each other but rather are considered to be complementary in memory formation. For instance, it has been shown, in hippocampus, that LTP and LTD have respective roles in encoding spatial information (Kemp and Manahan-Vaughan, 2004). LTD is necessary to acquire a new object location in a new environment while LTP is associated with spatial exploration. Other studies have suggested that LTD could contribute to the acquisition of new information by weakening previously strengthened synapses and by preventing interferences with this new incoming information (Etkin et al., 2006; Nicholls et al., 2008; Malleret et al., 2010).

Most of the studies conducted over the past decades relate to the plasticity of excitatory synapses and it is rather recently that attention has been focused on the plasticity of inhibitory synapses. In the following chapters, we will summarize the knowledge on these two aspects of long-term synaptic plasticity.

Plasticity of Excitatory Synapses

LTP

First discovered in hippocampus in the mid-eighties, LTP of excitatory synapses is generally considered as being a process requiring the activation of post (or pre) synaptic NMDA receptors and an increase in intracellular calcium that leads to an increase in synaptic efficacy after HFS of presynaptic terminals (Malenka and Nicoll, 1999). The most generally described mechanism to induce LTP is the activation of post-synaptic AMPA and NMDA receptors following a massive release of glutamate at the synaptic cleft induced by HFS of the presynaptic afferents. The activation of post-synaptic AMPA receptors results in a strong depolarization of the post-synaptic element and removes the magnesium blockade of the NMDA receptors (Kleckner and Dingledine, 1988; Burnashev et al., 1992; Calabresi et al., 1992) allowing cations to flow through the activated NMDA receptors. The high calcium permeability of NMDA receptors results in a calcium influx into the post-synaptic compartment that leads to changes in synaptic strength through a well described mechanism involving the activation of the calmodulin-dependent protein kinase

II (CaMKII) and the subsequent phosphorylation of AMPA receptors (increased open probability) and/or the trafficking of AMPA receptors to the post-synaptic membrane. Other kinases have been reported to be involved in the trafficking of AMPA receptors. Recent studies have shown that LTP can be induced at the presynaptic level either through a modulation of pre-synaptic NMDA receptors or through neuromodulators (NO, BDNF) released from the post-synaptic site acting at the presynaptic level. Following a theta-burst stimulation in hippocampus, McGuinness et al. (2010) have shown that action potentials at the synapse evoke a calcium influx through voltage-dependent calcium channel (VDCC) that induces glutamate release which can activate presynaptic NMDA receptors. This together with the removal of the Mg^{2+} block of NMDA receptors by depolarization results in an increase in intracellular calcium concentration and an enhanced glutamate release. Other mechanisms have been proposed to be responsible for the induction of LTP at excitatory synapses. The best characterized is the regulation of synaptic strength by retrograde messengers such as nitric oxide (NO). As shown in hippocampus, calcium ions entering the post-synaptic element through NMDA receptors activate NO synthase to produce NO from L-arginine. NO diffuses back to the presynaptic element and activates guanylate cyclase (GC) leading to the synthesis of cGMP and the activation of PKG and an increase in glutamate release (Costa et al., 2011). More recent studies reported that post-synaptic protein synthesis can also play a role in the regulation of the pre-synaptic mechanisms involved in persistent forms of LTP (Johnstone and Raymond, 2013). It has also been suggested that postsynaptic activation of the translation promotor mTOR complex 1 (mTORC1) results in the synthesis of the retrograde messenger BDNF and an enhancement of neurotransmitter release (Henry et al., 2012). Although NMDA receptors have a key role in the induction of LTP, it has been demonstrated in the visual cortex and in hippocampus (Johnston et al., 1992) that other players can trigger the calcium signal responsible for LTP induction. Grover and Teyler (1994) have shown that, in hippocampus, pairing presynaptic stimulation with post synaptic depolarization or with action potential firing results in a post synaptic calcium influx through L-type VDCC responsible for the induction of LTP. Other forms of NMDA-independent LTP have also been reported in rodent cortex that requires the activation of metabotropic glutamate receptors (Wilsch et al., 1998; Huemmeke et al., 2002).

LTD

The induction of LTD of excitatory synapses is mainly determined by the magnitude of the post-synaptic increase in intracellular calcium concentration (Mulkey and Malenka, 1992). A smaller increase in intracellular calcium concentration evoked by the activation of NMDA receptors will lead to the activation of a signaling cascade involving phosphatases such as calcineurin and PP1 (Lisman and Zhabotinsky, 2001) which results in the de-phosphorylation of synaptic AMPA receptors and their internalization causing a reduction of synaptic efficacy. Other forms of LTD involve the activation

of metabotropic glutamate receptors followed by an increase in intracellular calcium concentration. Depending on the receptor subtype different signaling pathways are engaged. In pyramidal neurons from the neocortex (Czarnecki et al., 2007), mGluR1 receptors activation causes an increase in intracellular calcium that leads to the activation of protein kinase C (PKC) and AMPA receptors internalization. It has also been suggested that activation of mGluR5 or mGluR1 receptors, respectively in *striatum* and in *nucleus accumbens*, results in an increase in post-synaptic calcium concentration and in the synthesis of endocannabinoids (eCBs) which activate presynaptic CB1R to decrease glutamate release (Chevalleyre et al., 2006). Finally another form of LTD has been described in visual cortex where LTD is induced by coincident activation of presynaptic NMDA auto-receptors and of CB1R, activated by retrograde signaling of eCBs (Sjöström et al., 2003).

Plasticity of Inhibitory Synapses

Post synaptic changes of GABAergic neurotransmission can be explained by: (i) a modulation of GABA receptors activity by protein kinases such as PKC, CaMKII or by phosphatases such as calcineurin (Kittler and Moss, 2003; Houston et al., 2009); (ii) trafficking of GABAA receptors at the synapse (Saliba et al., 2007; Arancibia-Cárcamo and Kittler, 2009; Castillo et al., 2011). As for excitatory synapses, modulations of postsynaptic calcium concentration are supposed to play a role in the induction of inhibitory synaptic plasticity. It has been demonstrated in hippocampus that LTP of inhibitory synaptic transmission is induced by an increase in post-synaptic calcium concentration resulting from the activation of GABAB receptors and the subsequent synthesis of IP3 leading to the release of calcium from the IP3-sensitive calcium store (Gaiarsa and Ben-Ari, 2006). It has also been demonstrated that, in the case of heterosynaptic plasticity, different sources of calcium (VGCC, ionotropic NMDA receptors, metabotropic mGluR1 glutamate receptors) contribute to the increases in post-synaptic calcium concentration responsible for changes in synaptic efficacy (Goldberg et al., 2003; Nyíri et al., 2003; Topolnik et al., 2005). This variety of post-synaptic calcium sources allows a precise control of calcium signaling and a fine tuning of synaptic plasticity (Camiré and Topolnik, 2012).

The best characterized form of presynaptic plasticity of GABAergic synapse involves the activation of presynaptic receptors by retrograde messengers such as: eCBs, BDNF and NO. eCB-mediated synaptic plasticity has been described in several brain regions such as hippocampus (Chevalleyre and Castillo, 2003), amygdala (Marsicano et al., 2002; Azad et al., 2004), *striatum* (Adermark and Lovinger, 2009), visual cortex (Jiang et al., 2010) and cerebellum (Pitler and Alger, 1992; Llano et al., 1994). The induction of eCB-mediated plasticity is initiated by glutamate release from presynaptic terminals which induces the post-synaptic synthesis of eCBs. eCBs retrogradely activate CB1R located on presynaptic afferents from GABAergic interneurons (heterosynaptic iLTD) to decrease GABA release

through a signaling cascade which inhibits the cAMP/protein kinase A (PKA) pathway (Heifets and Castillo, 2009). Whereas eCBs induce i-LTD, other retrograde messengers such as BDNF and NO can induce i-LTP. It has been shown in visual cortex and hippocampus (Lu, 2003; Gubellini et al., 2005; Sivakumaran et al., 2009) that the activation of NMDA receptors and/or VGCC and the subsequent increase in intracellular calcium concentration in the post synaptic element can result in the synthesis of BDNF or NO which increases GABA release (Nugent et al., 2007).

BALANCED NEURONAL NETWORKS

Neurons in the cerebral cortex consist of a majority of excitatory (glutamatergic) pyramidal neurons (75%–80%) making synaptic contacts both locally (local network) and over long distances (across distinct cortical areas) and of inhibitory (GABAergic) interneurons (25%–20%) making extensive local connections. Within a given local cortical network, neurons receive inputs from neighboring neurons which form recurrent excitatory and feedforward and feedback inhibitory circuits (Peters and Kara, 1985; White, 1989; Abeles, 1991; Markram et al., 2004). The great diversity of interneurons, in terms of their connectivity and their functional properties, allows them to control cortical excitation leading to a dynamic equilibrium between excitation and inhibition (Shu et al., 2003b). This dynamic control of excitation that regulates cortical network activity is performed through feedback and feedforward inhibition (Isaacson and Scanziani, 2011). Feedforward inhibition occurs when excitatory afferents activate first interneurons, prior to activating principal neurons, and results in a reduced excitation of the target neuron. This well described mechanism (Isaacson and Scanziani, 2011) contributes to the weakening of excitatory inputs. Feedback inhibition takes place when active principal neurons excite inhibitory interneurons which, in a feedback loop, inhibit principal neurons themselves (for instance, see Silberberg and Markram, 2007; Berger et al., 2010) to ensure the stability to the network.

It is remarkable to note that despite the diversity of neuronal networks, the relative contribution of excitatory and inhibitory input conductance to a given neuron is dynamically maintained at comparable values across different cortical layers and different cortical areas to guarantee a proper balance between excitation and inhibition (E-I balance). The E-I balance, determined as the ratio between excitatory and inhibitory input conductance onto a neuron evoked by an electrical stimulation of afferents (*in vitro*) or by sensory stimuli (*in vivo*), is maintained at approximately 20% excitation and 80% inhibition (Le Roux et al., 2006; Monier et al., 2008; Lucas-Meunier et al., 2009; Zhang et al., 2011; Xue et al., 2014; den Boon et al., 2015). This dynamic E-I balance is thought to result from the coordinated activities of direct and recurrent excitation and (feed-forward and feedback) inhibition and reflects the activity of neuronal networks at a given moment (Haider and McCormick, 2009; Isaacson and Scanziani, 2011). A proper balance between excitatory and inhibitory inputs onto cortical neurons is essential

to maintain the stability of cortical networks in order to perform cognitive functions such as memory and sensory information processing. For instance, it determines proper cortical network rhythms responsible for higher order cognitive functions (Shu et al., 2003b; Haider et al., 2006). It is also essential for physiological processes such as short term memory and long term memory (Saghatelian et al., 2001; Egorov et al., 2002). Cortical responses elaborated by L5PyNs depend on the balance between excitatory and inhibitory inputs perceived (Borg-Graham et al., 1998; Wehr and Zador, 2003). Balanced excitatory and inhibitory neurotransmission also appears to be fundamental in the fine tuning of neuronal responses to specific sensory features.

It is conceivable to think that any alterations of excitation or inhibition will generate aberrant information processing in the cortex (Haider and McCormick, 2009) and will lead to pathological situations. Indeed, disturbances in the E-I balance are associated with a broad spectrum of neuropsychiatric and neurological diseases, such as autism, schizophrenia and epilepsy (Cobos et al., 2005; Lewis et al., 2005; Rubenstein, 2010). It has been observed that, in epilepsy, an altered maturation of chandelier cells (interneurons) interferes with the activity of pyramidal neurons (Marco et al., 1996), leading to an unbalanced E-I ratio (Cossart et al., 2005). It is also hypothesized that, in schizophrenia, a dysfunction of NMDA receptors (Coyle, 2006) changes the level of excitation and consequently the E-I balance (Kehrer et al., 2008). Finally, a dysregulation of the E-I balance has also been observed in autism (Rubenstein and Merzenich, 2003; Powell, 2004; Rippon et al., 2007), Rett syndrome (Dani et al., 2005) and Tourette syndrome (Singer and Minzer, 2003).

Given that neuronal networks require a proper E-I balance to perform cognitive functions, how does network stability deal with synaptic plasticity? In other words, how to learn within dynamically balanced networks? The learning process might not only be considered not only as a gain or a loss of efficacy at a given synapse but also as dynamic changes of both excitatory and inhibitory synaptic strength. This homeostatic maintenance of excitation and inhibition balance may be a determining factor in the regulation of neuronal input-output function and information processing (learning) within a given neuronal network (Daoudal and Debanne, 2003; Staff and Spruston, 2003; Marder and Buonomano, 2004). Although the effects of concerted regulation of excitation and inhibition are still poorly understood, it has been suggested that balanced or imbalanced changes in synaptic strength of excitatory and inhibitory inputs have a different impact on the neuronal input-output function and consequently on neuronal firing. Indeed the two parameters, threshold and gain (rate of change or sensitivity of the input-output function), that characterize the probability of a neuron to fire action potentials as a function of stimulus intensity can be modulated by the ratio between excitation and inhibition. By combining a computational model with experimental data obtained in hippocampus, Carvalho and Buonomano (2009) have shown that imbalanced plasticity of excitatory synaptic inputs affects the threshold while the E-I balance affect the gain allowing neurons to optimize their information processing.

The method we use to determine the E-I balance is based on the continuous measurement of evoked postsynaptic currents and the decomposition of the conductance dynamics into its excitatory and inhibitory components (Monier et al., 2003, 2008). This continuous and simultaneous determination of both excitatory and inhibitory inputs also offers the possibility to determine the changes in excitatory and inhibitory synaptic strength occurring after applying a high frequency stimulus evoking long-term synaptic plasticity. We have shown that, in rat visual cortex and in mouse PFC, HFSs of layer 2–3 (theta-burst stimulation), not only induced LTP of excitatory inputs measured from L5PyNs but also LTP of inhibitory inputs resulting in an E-I balance that remains equal to the control situation (Le Roux et al., 2006; Meunier et al., 2013). These results are in accordance with the notion of homeostatic regulation which mainly involves a dynamic adjustment of excitatory and inhibitory circuits (Turrigiano and Nelson, 2004). Because alterations in several neurotransmitter systems have been correlated with cognitive deficits resulting in impairments of learning and memory, we will focus our attention on the importance of the cooperation between different neuromodulators in the modulation of the plasticity of excitatory and inhibitory synapses. Based on our recent findings, we will highlight the importance of the coordinated action of 5-HT and DA in regulating the interaction between excitation and inhibition in the PFC, a cortical area involved in higher order cognitive functions.

TUNING THE PLASTICITY

Serotonin as a Modulator

5-HT is the most widely distributed neuromodulator in the brain (Dahlström and Fuxe, 1964; Steinbusch, 1981). 5-HT is implicated in the regulation of many physiological functions such as mood, sleep, vigilance, cognitive functions, learning and memory. In the brain, serotonergic axons originating from the raphe nucleus make synapses “en passant” and release 5-HT from varicosities (Oleskevich and Descarries, 1990) to activate a great diversity of 5-HT receptors (up to 16 types of receptors have been identified; Bockaert et al., 2006). We will focus here our attention on the role of the metabotropic 5-HT_{1A} receptor (5-HT_{1A}R) which is predominant in the PFC (Santana et al., 2004).

5-HT_{1A}Rs have been identified both on serotonergic neurons (autoreceptors) where they regulate the release of 5-HT through a negative feedback and on neuronal targets of serotonergic neurons where they function as heteroreceptors. In the cortex, the majority of postsynaptic 5-HT_{1A}Rs (50%–60%) are expressed in glutamatergic neurons. In L5PyNs, 5-HT_{1A}Rs are located in the soma, in the initial axonal part (Czyrak et al., 2003; Cruz et al., 2004; Santana et al., 2004) and in dendrites (Kia et al., 1996; Riad et al., 2000). We have shown for instance that in the cerebral cortex this specific distribution of 5-HTRs on pyramidal neurons is important to control output signals from the cortex (Moreau et al., 2010). In the PFC, a weaker proportion (25%) of 5-HT_{1A}Rs is also expressed in GABAergic interneurons projecting onto

the dendrites of pyramidal cells (Santana et al., 2004). From this distribution of 5-HT_{1A}Rs in the PFC, it appears that 5-HT can regulate the excitability of both glutamatergic and GABAergic neurons (Andrade, 2011; Puig and Gullledge, 2011) but the modulatory effects of 5-HT_{1A}Rs activation are not clearly understood.

Several pathologies such as mood disorders, anxiety, psychosis and fear are associated with serotonergic disorders and dysfunction of 5-HT_{1A}Rs. For instance, it has been shown that the number of postsynaptic 5-HT_{1A}Rs is decreased in depressive or anxious human brain (Shively et al., 2006; Lanzenberger et al., 2007; Akimova et al., 2009). One of the most commonly used pharmacological treatments of anxiety disorders is the use of selective serotonin reuptake inhibitors (SSRIs; Kasper et al., 2005). However, failures in SSRI treatment seems to be associated with the polymorphism of the gene encoding 5-HT_{1A}R (Lemondé et al., 2003; Czesak et al., 2012) which might differently affect the nature (or type) of pre- vs. post-synaptic 5-HT_{1A}R (Bortolozzi et al., 2012). A better understanding of the role of post-synaptic 5-HT_{1A}R in the PFC is a prerequisite to the design of more selective psychoactive drugs.

Dopamine as a Modulator

Dopaminergic fibers, mainly originating from the *Substantia nigra*, are widely distributed in all areas of the PFC and target layer 2 and layer 5 (Emson and Koob, 1978; Callier et al., 2003; Van De Werd et al., 2010). The effects of DA are mediated by the D1-class receptors (D1 and D5 receptors) and by the D2-class receptors (D2, D3 and D4 receptors; Beaulieu and Gainetdinov, 2011). Activation of the D1 class enhances the activity of adenylate cyclase whereas activation of the D2 class inhibits it (Girault and Greengard, 2004). In rat PFC, D1-like receptors (D1Rs) and D2Rs are localized on dendritic spines of L5PyNs (Gaspar et al., 1995; Negyessy and Goldman-Rakic, 2005; Paspalas and Goldman-Rakic, 2005). D2Rs are also present on GABAergic interneurons (Santana et al., 2009) while D1Rs are mainly expressed in the parvalbumin-positive subtype of GABAergic interneurons (Glausier et al., 2009). Such a distribution of D1 and D2 receptors is again in favor of a modulatory role of DA on neuronal networks in the PFC.

Many electrophysiological studies have shown that activation of DA D1Rs favors the induction of LTP at hippocampal-PFC synapses by increasing NMDAR-mediated responses in PFC (Gurden et al., 2000; Chen et al., 2004). This enhancement of NMDA current (Shih, 2004; Tseng and O'Donnell, 2004) is explained by either the externalization of NMDA receptors (Dunah and Standaert, 2001; Dunah et al., 2004) or by their phosphorylation. D1Rs and NMDAR are co-localized in pyramidal neurons of the PFC and a direct interaction between the C-terminal domain of D1R and NR1-NR2A subunits of the NMDAR has been proposed to explain the increase in NMDA current (Kruse et al., 2009). Activation of D2Rs results in a decrease in NMDA currents (Zheng et al., 1999; Wang et al., 2003) presumably through the inhibition of the CaMKII by the PKA and the subsequent internalization of

NMDARs (Wang et al., 2003). Alternatively, another signaling cascade leading to the internalization of the NR2B subunit of the NMDAR and a decrease in NMDA current has been proposed. It involves, in the PFC, an increase in the activity of the glycogen-synthase kinase-3 (GSK3) after D2R activation (Beaulieu et al., 2008; Li et al., 2009; Skinbjerg et al., 2009; Beaulieu and Gainetdinov, 2011; Sutton and Rushlow, 2011).

It is of particular interest to note that in the treatment of schizophrenia, new therapeutic strategies consist in targeting both 5-HT_{1A}Rs and DA receptors by combining either 5-HT_{1A}Rs agonists with D2Rs antagonists (Newman-Tancredi, 2010) or 5-HT_{1A} agonists with a D1R agonist and a D2R antagonist to prevent positive and negative symptoms of schizophrenia (Newman-Tancredi and Kleven, 2011). These clinical observations, highlight the importance of taking into account the interactions between serotonergic and dopaminergic systems and their consequences on the physiology of the PFC, a brain area particularly associated with depressive disorders and schizophrenia.

Complex Interactions Between Modulators of the Plasticity in the PFC

5-HT, through the activation of postsynaptic 5-HT_{1A}R, is known to regulate the excitability of glutamatergic and GABAergic neurons in the PFC (Andrade, 2011; Puig and Gullledge, 2011). 5-HT modulates the induction of plasticity, depending on the 5-HT receptor subtype and brain regions (Kemp and Manahan-Vaughan, 2004). In the rat PFC, consequences of HFS on synaptic plasticity are rather complicated given that tetanic stimulations in superficial layers can induce either LTP or LTD or no plasticity. Indeed, it has been reported that such a HFS protocol can induce LTD in about one half of the cells and LTP in about one third of the cells, the remaining cells did not display any change of synaptic properties (Hirsch and Crepel, 1990, 1991; Nowicky and Bindman, 1993; Matsuda et al., 2006).

5-HT_{1A} Receptors Direct the Orientation of Plasticity in Layer5 Pyramidal Neurons of the PFC

To explore the role of 5-HT_{1A}Rs in the modulation of the plasticity of excitatory and inhibitory synaptic inputs to L5PyNs of the PFC, we compared the excitatory and inhibitory conductances evoked by electrical stimulations of layer 2/3 between wild-type (129/Sv WT) and 5-HT_{1A}R-knock out (5-HT_{1A}R-KO) mice. These transgenic mice are considered as a model for anxiety disorder (Ramboz et al., 1998) and have been designed to better understand human psychiatric conditions where a profound decrease of 5-HT_{1A}R expression has been demonstrated (Sargent et al., 2000; Bhagwagar et al., 2004; Shively et al., 2006; Lanzenberger et al., 2007; Akimova et al., 2009).

Our experimental approach, based on the simultaneous determination of excitatory (E) and inhibitory (I) conductance in L5PyNs, also allows the determination of the E-I balance in the PFC. Electrical stimulations of layer 2/3 (low frequency stimulation, 0.05 Hz) evoked complex postsynaptic current in

L5PyNs (**Figure 1A**). The evoked total synaptic conductance (gT) was extracted (see Le Roux et al., 2006) and decomposed into excitatory (gE) and inhibitory (gI) conductance (**Figure 1A**). This allowed further evaluation of the relative contribution of evoked excitatory and inhibitory inputs reaching the soma of the recorded pyramidal neuron (Le Roux et al., 2006; Moreau et al., 2010). Calculated integrals of excitatory (IntgE) and inhibitory (IntgI) conductance were expressed as percentages of the integral of the total conductance (IntgT; **Figure 1B**). Analysis of recorded neurons showed that the E-I balance was significantly different in 5-HT_{1A}R-KO mutants (23%–77%) compared to 129/Sv WT mice (20%–80%; **Figure 1B**). In control 129/Sv WT mice and in the presence of WAY 100635 (a 5-HT_{1A}R selective antagonist) the E-I balance was shifted towards more excitation (24%–76%), a value similar to what we observed in 5HT_{1A}R-KO mice (Meunier et al., 2013). These results show that L5PyNs in 129/Sv mice express functional 5HT_{1A}Rs and that 5HT_{1A}Rs play a crucial role in tuning the E-I balance in L5PyNs of the PFC.

We observed that, in both strains, HFS (theta burst) induced either LTP or LTD of both excitatory and inhibitory conductance or no plasticity (**Figure 1C**). These changes in synaptic efficacy were due to the activation of NMDARs since their blockade with D-L-AP5 prevented the induction of synaptic plasticity. When comparing 129/Sv WT and 5HT_{1A}R-KO mice showing LTP of excitatory and inhibitory synaptic transmission, we observed that the absence of functional 5HT_{1A}R resulted in a reduced potentiation of excitatory synaptic transmission while the potentiation of inhibition remained unaffected (Meunier et al., 2013). The use of a specific 5-HT_{1A}R antagonist confirmed the role of 5-HT_{1A}Rs in the modulation of LTP of excitation in the PFC. We also observed that the proportion (calculated from the whole neuronal population) of L5PyNs displaying either LTP or LTD or no change were different between 129/Sv WT and 5-HT_{1A}R-KO mice. In 5-HT_{1A}R-KO mice, the percentage of neurons displaying LTP was significantly increased compared to 129/Sv WT mice (**Figure 2**) whereas the percentage of neurons showing LTD remained identical. Our results indicate

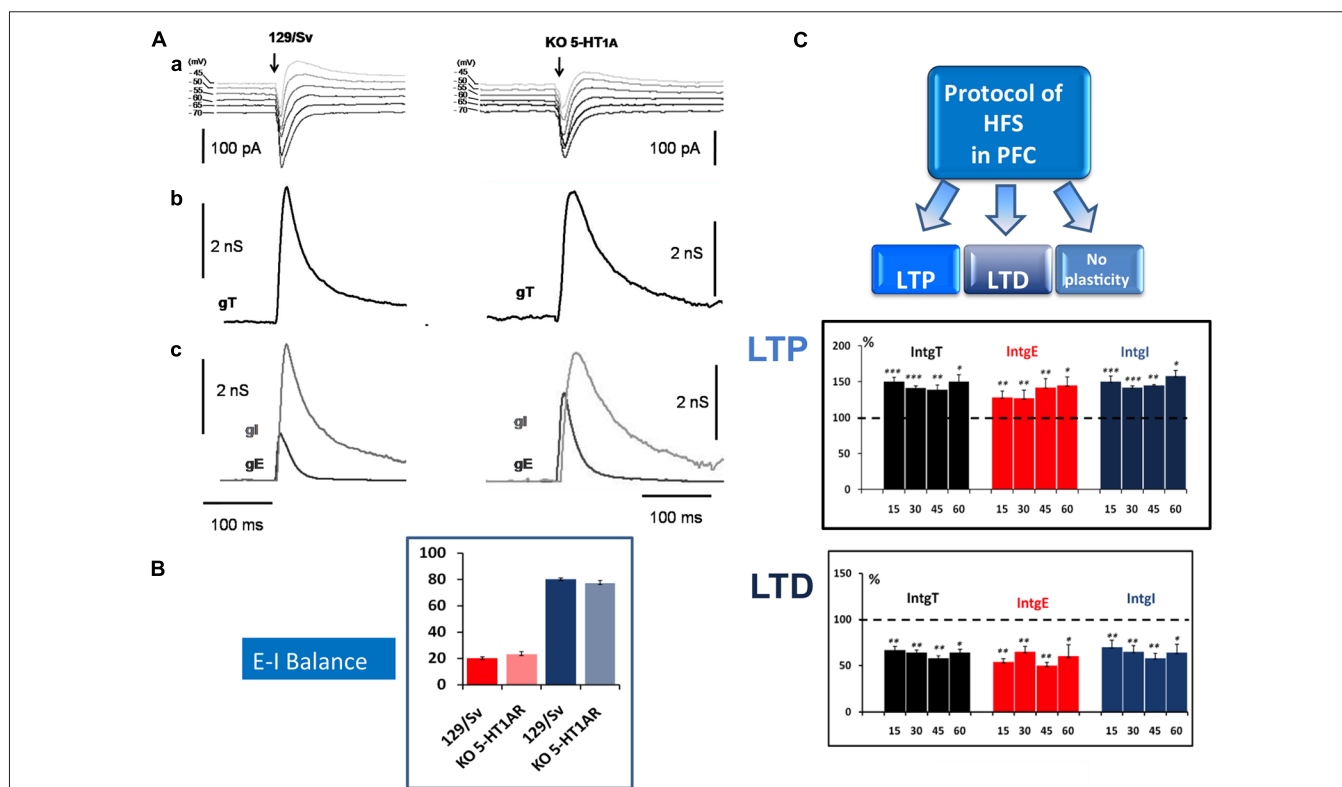
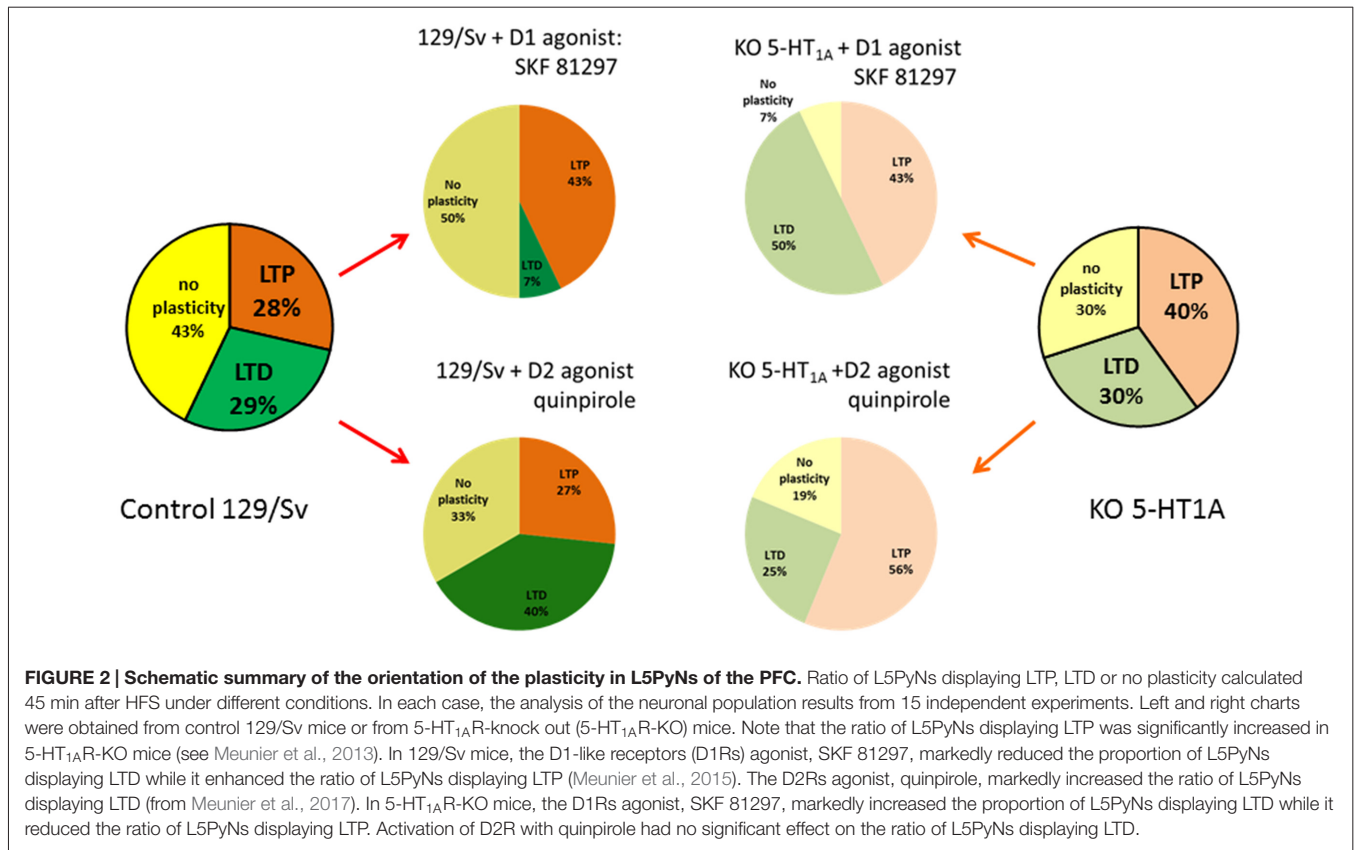


FIGURE 1 | Determination of the Excitation-Inhibition balance (E-I balance) in the prefrontal cortex (PFC) and analysis of synaptic plasticity. (A) Brief description of the method to determine the E-I balance. **(a)** Representative current traces of synaptic responses (upper part) to layer 2–3 stimulation (arrow) recorded from a layer 5 pyramidal neuron (L5PyN) under voltage-clamp at various holding potentials in 129/Sv and KO 5-HT_{1A} mice. **(b)** The second row represents the corresponding total conductance changes (gT) at the somatic level (for a complete description of the method, see Le Roux et al., 2006; Lucas-Meunier et al., 2009). **(c)** gT was then decomposed into its Excitatory (gE) and the Inhibitory (gI) components (third row). **(B)** The percentage of excitation and inhibition is expressed as the ratio of its integral value integrals of excitatory (IntgE) and inhibitory (IntgI) to the total conductance IntgT to determine the E-I balance. We observed a significant shift of the E-I balance towards more excitation between 129/Sv mice (20%–80%) and 5-HT_{1A}R-KO mice (23%–77%; Meunier et al., 2013). **(C)** High frequency stimulation (HFS) protocol (Theta burst) in layer 2–3 of the PFC induced in L5PyNs, long term potentiation (LTP) or long term depression (LTD) or no plasticity of the responses. LTP (upper insert) was recorded 15 min, 30 min, 45 min and 60 min after the stimulation. Histograms represent relative changes (compared to the control before HFS: 100%) of IntgT, IntgE, IntgI. Synaptic conductances were determined under control conditions or after HFS protocol with a low frequency of stimulation (0.05 Hz). LTD (lower insert) was recorded in the same condition. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



that 5-HT_{1A}Rs play an important role in the orientation of the synaptic plasticity of L5PyNs in the PFC towards either LTP or LTD or no plasticity (Meunier et al., 2013).

It is established that different forms of synaptic plasticity such as LTP and LTD are induced by NMDAR activation (Stanton, 1996) that leads to the control of the trafficking of AMPA receptors. The externalization (Malenka and Nicoll, 1999; Malinow and Malenka, 2002) or the internalization (Beattie et al., 2000; Hanley and Henley, 2005; Fernández-Monreal et al., 2012) of AMPA receptors are commonly considered to be responsible for LTP and LTD induction respectively. The orientation of the synaptic plasticity towards LTP or LTD relying on AMPARs trafficking is known to be correlated with the magnitude of the dendritic calcium signal (Cormier et al., 2001). We observed that the activation of 5-HT_{1A}Rs enhanced evoked NMDA currents, indicating that 5-HT_{1A}Rs modulate NMDARs (Meunier et al., 2013). Therefore we propose that the increase in the percentage of neurons displaying LTP observed in the absence of functional 5-HT_{1A}Rs (5-HT_{1A}R-KO mice) could result from a reduced calcium influx through NMDARs. So it appears that, in the PFC, 5-HT_{1A}Rs limit the induction of LTP and favor LTD by modulating the NMDA currents.

D1R-Mediated Modulation of Synaptic Plasticity Depends on Functional 5HT_{1A}R

At hippocampal-PFC synapses, DA (acting at D1Rs) is known to favor LTP induction (Gurden et al., 2000; Chen

et al., 2004). We have shown recently (Meunier et al., 2015) that a high frequency protocol of stimulation (HFS) in the presence of the D1R agonist SKF 81297 results in an increase of the population of L5PyNs displaying LTP in 129/Sv mice (Figure 2). By contrast, we observed an increase in the amount of neurons showing LTD when D1R were activated in the absence of functional 5-HT_{1A}Rs (KO). This cooperation between 5-HT_{1A}Rs and D1Rs to determine the direction of the synaptic plasticity was confirmed by a pharmacological approach (Meunier et al., 2015). We also observed in 129/Sv mice, an increase in the number of L5PyNs in the “no plasticity” class after D1Rs activation (Figure 2).

This orientation of the plasticity could be the result of a modulation of NMDA-mediated currents by D1Rs and 5-HT_{1A}Rs. A strong increase in intracellular calcium concentration within the dendritic spines of L5PyNs would facilitate LTP induction whereas a weaker calcium signal would facilitate LTD induction. D1Rs activation is known to modulate NMDARs and this modulation relies on the expression of different NMDARs subunits (NR2B vs. NR2A; Liu et al., 2006; Varela et al., 2009). The subunit composition of NMDARs determines the amplitude and the duration of the transient calcium signal that will lead direct synaptic plasticity towards either LTP or LTD (Mulkey and Malenka, 1992; Huang et al., 2010). We therefore make the assumption that the cooperation between 5-HT_{1A}Rs and D1Rs would set the magnitude of the

calcium influx through NMDARs (Meunier et al., 2015). The resulting calcium signal at the dendrite would lead to the modulation of the CamKII activity (Chen et al., 2007; Ashpole et al., 2012; Coultrap et al., 2014) to control the trafficking of AMPARs at the synapse and consequently determine the direction of the synaptic plasticity. When D1Rs are activated in the absence of functional 5-HT_{1A}Rs (5-HT_{1A}R-KO mice), the increased proportion of neurons showing LTD responses (Meunier et al., 2015) could then be the result of reduced NMDA currents due to changes in NMDARs subunits composition.

It cannot be excluded that other signaling pathways following 5-HT_{1A}Rs and D1Rs activation play a role in AMPARs trafficking and in the modulation of synaptic plasticity. Following 5-HT_{1A}R activation (Polter and Li, 2010) as well as D1R activation (Gurden et al., 2000; Huang et al., 2004; Kruse et al., 2009), the cAMP/PKA signaling cascade could also be involved in regulating the incorporation of AMPARs at the synapse.

There is also growing evidence that D1/D5R stimulation leads to Gq-dependent activation of PLC, IP3-mediated Ca²⁺ release and CamKII activation (Chen et al., 2007). It is important to note that several studies have reported that metabotropic receptor activation coupled to PLC stimulation lead to LTD induction (Choi et al., 2005). In the 5-HT_{1A}Rs-KO mice, the D1Rs effects could mostly rely on the regulation of PLC activity.

Activation of D2R in the Presence of Functional 5-HT_{1A}Rs Promotes HFS-Induced LTD of Excitatory Synapses via the Activation of GSK3

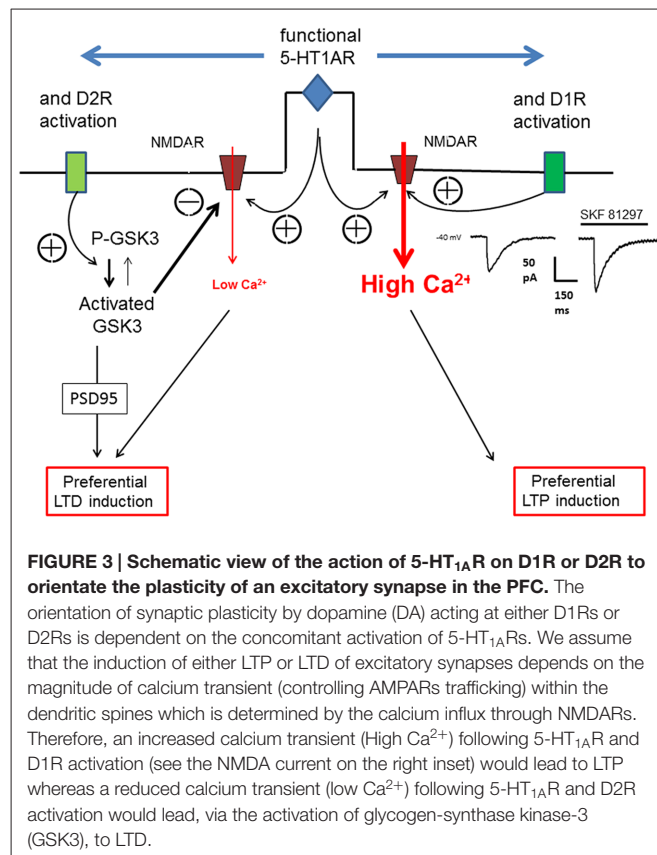
DA is known to modulate NMDAR- and AMPAR-mediated currents, neuronal excitability and synaptic plasticity towards LTD through the activation of D2Rs. Both DA and 5-HT can regulate neuronal activity via a common signaling pathway involving the regulation of the activity of GSK3, a serine/threonine kinase playing an important role in the regulation of several receptors for neurotransmitters (Chen et al., 2009).

Two isoforms of GSK3 have been identified (GSK3 α and GSK3 β ; Woodgett, 1990, 2001) which can be inactivated through their phosphorylation by Akt (Cross et al., 1995; Frame et al., 2001). It has been reported that, in the PFC and the striatum, the activation of D2Rs induces the activation of GSK3 (Beaulieu et al., 2004, 2008; Chen et al., 2009; Beaulieu and Gainetdinov, 2011). This activation of GSK3 β has been shown to promote the internalization of the NR2B subunit of NMDARs leading in the rat hippocampus to the induction of LTD (Peineau et al., 2007) while LTP could be favored by higher levels of phosphorylation of GSK3 β (Hooper et al., 2007; Peineau et al., 2007). It has also been observed that GSK3 can modulate NMDARs and AMPARs through either 5-HT_{1A}R or 5-HT_{2A}R activation (Li et al., 2004, 2007).

Importantly, like 5-HT_{1A}Rs and D2Rs, GSK3 is also a molecular target in the treatment of neuropsychiatric disorders such as major depression and anxiety (Meltzer et al., 2003; Meltzer and Massey, 2011). We therefore investigated the possible cooperation between 5-HT_{1A}R and D2R in the modulation of synaptic plasticity within the PFC. We have

shown that the activation of D2Rs and the downstream activation of GSK3 favor the induction of LTD of excitatory synaptic transmission (Meunier et al., 2017). In addition, we demonstrated that this control of synaptic plasticity via GSK3 requires the presence of functional 5-HT_{1A}Rs. We therefore made the hypothesis of cooperation between 5-HT_{1A}R and D2R, via the regulation of GSK3, to modulate excitatory synaptic transmission. This hypothesis is supported by recent observations showing that D2R and 5-HT_{1A}R can modulate the phosphorylation or the dephosphorylation of GSK3 β (the dephosphorylated form being the active form).

The pathway downstream D2R activation leads, via the regulation of cyclic AMP production and β -arrestin activity, to the dephosphorylation (deactivation) of Akt and consequently to the dephosphorylation (activation) of GSK3 by the protein phosphatase 2A (PP2A Beaulieu et al., 2004, 2005, 2008, 2009; Beurel et al., 2015). There are apparent contradictory observations regarding the regulation of GSK3 β by 5-HT receptors. It has been reported, in rat hippocampus, that the activation of 5-HT_{1A}Rs increases the phosphorylation of GSK3 β by Akt, promoting the inactivated form (Polter et al., 2012). Others have suggested that 5-HT_{1A}Rs activation could activate GSK3 via the phosphorylation of Akt by PP2A (Hsiung et al., 2008). We have shown, in the PFC of 5-HT_{1A}R-KO mice, an increase in the phosphorylated form of GSK3 (Meunier et al., 2017). This suggests that in the PFC, the activation of 5-HT_{1A}Rs promotes the active form of GSK3 and leads to the internalization of AMPARs and to the induction of LTD of excitatory synapses.



Our results highlight the importance of the cooperation between D2Rs and 5-HT_{1A}Rs in the regulation of the E-I balance and of the plasticity of excitatory synapses in the PFC. 5-HT_{2A}R activation is also known to have a clear excitatory effect on L5PyNs and layer 2–3 GABAergic interneurons in the PFC (Andrade, 2011; Celada et al., 2013) to modulate NMDARs and AMPARs through GSK3 (Li et al., 2004, 2007). It is thus very likely that 5-HT_{2A}R activation plays a role in the modulation of the E-I balance and in the modulation of long-term synaptic plasticity by DA. The functional dimerization between D2R and 5-HT_{2A}R (Franklin and Carrasco, 2012) that can be modulated by cannabinoid receptors, introduces another level of complexity that has to be taken in account. Recent findings indicate a prominent co-localization of D2Rs and 5-HT_{1A}Rs in the neurons of the PFC compared to other brain regions (Łukasiewicz et al., 2016) suggesting that D2Rs-5-HT_{1A}Rs heteromers may be expressed in the PFC. When expressed in HEK cells (Łukasiewicz et al., 2016), it appears that the activation of such heteromers recruits metabolic pathways different from those downstream the activation of homomeric 5-HT_{1A} or D2 receptors. This could open up new therapeutic strategies based on the selective activation of one or the other metabolic pathways to improve the treatment of pathologies such as schizophrenia.

Schematic Overview and Perspectives

Based on our own research, we focused here our attention on the role of 5-HT_{1A}Rs in the dopaminergic modulation of long-term synaptic plasticity. The modulatory effect of D1 or D2R on excitatory synaptic plasticity depends on the presence of functional 5-HT_{1A}Rs. It appears that 5-HT_{1A}R cooperate with either D1R or D2R to direct the long term plasticity towards either LTP (D1Rs) or LTD (D2R). We assume that it is the cooperation of 5-HT_{1A}Rs with either D1Rs or D2Rs that will determine the magnitude of the Ca²⁺ influx through NMDARs evoked by high frequency synaptic stimulation and consequently favor either LTP or LTD. As illustrated in **Figure 3**, we consider the Ca²⁺ transient within dendritic spines as a key element of long-term synaptic plasticity. However it remains to

determine how the recruitment of different signaling pathways following the activation of D1Rs, D2Rs and 5-HT_{1A}Rs leads to the regulation of AMPAR trafficking at the synapse which determines the synaptic strength. The cooperation between 5-HT and DA receptors in the modulation of the long-term plasticity of excitatory synaptic inputs may have consequences on neuronal output (spiking behavior) and information processing within the PFC. The absence of modulatory effects on inhibitory synaptic inputs would result in imbalanced changes in synaptic strength in favor of excitation affecting the threshold of neuronal input-output functions (Carvalho and Buonomano, 2009).

GSK3 β is considered as a key player in synaptic plasticity (reviewed in Bradley et al., 2012). It is therefore important to understand the factors regulating GSK3 β activity in the perspective of adapting therapy for several neurological and psychiatric disorders in which a dysregulation of GSK3 β activity has been reported (Beurel et al., 2015). Mood disorders (major depressive disorder and bipolar disorder) are characterized by a disruption of the fine equilibrium between 5-HT and DA systems regulating the balance between the inactive and the active form of GSK3 β at the synaptic level. Many therapeutic strategies using Li⁺ as a blocker of GSK3 β activity have been considered as an attempt to reset such a balance (Jope, 2011). Our results suggest that in the case of pathologies such as major depression for which a reduction of the number of 5-HT_{1A}Rs is observed, new therapeutic strategies resetting the equilibrium between the active and the inactive form of GSK3 β could rather consist in acting at both 5-HT and DA receptors.

AUTHOR CONTRIBUTIONS

CNJM designed and conducted the experiments, wrote the article. PC wrote the article. PMF designed the experiments and wrote the article.

FUNDING

Centre National de la Recherche Scientifique (CNRS) is our institution which has provided basic funding.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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