Review

Cartography of 5-HT1A and 5-HT2A receptor subtypes in prefrontal cortex and its projections

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Cartography of 5-HT_{1A} and 5-HT_{2A} receptor subtypes in prefrontal cortex and its projections

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Abstract

Since the development of chemical neuroanatomical tools in the 1960's, a tremendous wealth of information has been generated on the anatomical components of the serotonergic system, at the microscopic level in the brain including the prefrontal cortex (PFC). The PFC receives a widespread distribution of serotonin (5-hydroxitryptamine, 5-HT) terminals from the median and dorsal raphe nuclei. 5-HT receptors were first visualized using radioligand autoradiography in the late 1980's and early 1990's and showed, in contrast to 5-HT innervation, a differential distribution of binding sites associated with different 5-HT receptor subtypes. Due to the cloning of the different 5-HT receptor subtype genes in the late 1980's and early 1990's it was possible, using *in situ* hybridization histochemistry, to localize cells expressing mRNA for these receptors. Double *in situ* hybridization histochemistry and immunohistochemistry allowed for the chemical characterization of the phenotype of cells expressing 5-HT receptors. Tract tracing technology allowed a detailed cartography of the neuronal connections of PFC and other brain areas. Based on these data, maps have been constructed that reflect our current understanding of the different circuits where 5-HT receptors can modulate the electrophysiological, pharmacological and behavioral functions of the PFC.

We will review current knowledge regarding the cellular localization of 5-HT_{1A} and 5-HT_{2A} receptors in mammalian PFC and their possible functions in the neuronal circuits of the PFC. We will discuss data generated in our laboratory as well as in others, focusing on localization in the pyramidal and GABAergic neuronal cell populations in different mammalian species using molecular neuroanatomy and on the connections with other brain regions.

Keywords: cytoarchitecture, pyramidal cells, GABAergic cells, neuronal circuits,

INTRODUCTION

In the last 20 years our laboratory has focused on understanding serotonin receptors in the brain. For that, we have used different technologies with a particular emphasis in the elucidation of the regional and cellular distribution of these receptors using molecular probes and with resolution at the light microscopic level. In this way we generate molecular, anatomical maps that describe the localization and origin of serotonin receptors in different cellular types. From there, we try to understand the role of the different receptors in the modulation of the functions of a particular brain circuit. To correlate findings in experimental animals with humans, we compare these maps in several species.

The majority of serotonin (5-hydroxytryptamine, 5-HT) is produced in the periphery, in non-neuronal tissues in the gastrointestinal tract, cardiovascular system and blood, but it is also synthesized in the central nervous system (CNS). Brain 5-HT has been implicated in the pathophysiology and treatment of psychiatric disorders. 5-HT exerts its actions by interacting with diverse membrane-bound receptor families of the G-protein-coupled receptor family of which today six families have been identified, 5-HT_1, 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7, and the ligand-gated ion channel family, composed by 5-HT_3 [1,2].

The prefrontal cortex (PFC), located in the anterior part of the frontal lobe, presents variations across species, especially in the amount of granular versus agranular cortices [3]. In primates, the PFC comprises areas 8–13, 24, 25, 32 and 44–47 according to Brodmann [4]. The dorsal PFC refers to Brodmann's area (BA) 8-10; the dorsolateral PFC, to BA 46; ventral PFC, to BA 9; lateral PFC, to BA 44, 45 and 47; the orbitofrontal PFC, to areas BA 11 and 12; anterior cingulate region, to BA 24 and 25; and the cortex of medial surface, to BA 32 [5-7]. Rat PFC is exclusively composed of agranular cortical areas and comprises the medial PFC (including anterior cingulate, prelimbic, and infralimbic regions), the orbital PFC (ventral and lateral regions) and motor areas (primary and secondary) [8].

The PFC orchestrates in primates complex actions (concepts of action, planning of complex cognitive and affective functions, and programs) but also plays a role in the operations for their enactment, including working memory [6,9] and is hence implicated in mood disorders [10,11]. The PFC develops late and receives fiber connections from numerous subcortical and limbic structures, as well as from other neocortical areas, most of these connections being reciprocal (see Groenewegen and Uylings for review)[12]. It receives serotonergic innervation from the median and dorsal raphe nuclei [13-15] and sends glutamatergic projections to these raphe nuclei [16-18]. In the rat, PFC projections to medullary raphe nuclei have been also described [19]. There is a high degree of connections between the different parts of the PFC: each PFC region (orbital, medial and lateral) is connected to itself and to the other two; the connectivity is interhemispheric and mainly organized in a reciprocal and topographical manner [20]. The cortico-cortical connections originate and terminate in upper cortical layers II and III [21].

In the PFC, as in the other cortical regions, there are two main types of intrinsic neurons, classified according to the neurotransmitter synthesized, glutamate or gamma-aminobutyric acid (GABA) as: glutamatergic and GABAergic cells. The glutamatergic cells are the pyramidal and spiny stellate cells characterized by the excitatory asymmetric synapses they form. The majority of cortical neurons are pyramidal output neurons located in layers II-VI. Harris and Shepherd [22] differentiate 3 types of excitatory cells in the neocortex: i) intratelencephalic neurons, found in layers II-VI and projecting exclusively to the telencephalon; ii) pyramidal tract neurons, located in layer V and projecting to brainstem, neocortex, striatum and thalamus; and iii) corticothalamic neurons found in layer VI.

The GABAergic cells are smooth or sparsely spiny interneurons forming inhibitory symmetric synapses and found in layers I-VI. GABAergic interneurons are composed by a large diversity of different cells types which

have been classically classified from their firing pattern, their morphology, cell biochemical markers, as well as their synaptic targets [23-25]. The Petilla terminology [26] divides cortical GABAergic interneurons by several features: morphological (soma, dendrite, axon and connections), molecular (expression of specific molecular markers) and physiological and biophysical features. More recently, cortical GABAergic interneurons have been classified basically according to the axonal arborization pattern [27] into several classes: their distribution in cortex and cortical columns, relative location of the axon and dendritic arbors, the recognizable morphological characteristics commonly used in the literature. Kepecs and Fishell [28] in a recent review propose that the different properties of the interneurons found across the brain may arise from a small number of distinct cardinal classes, and that interneuronal diversity could derive from telencephalic interneuron progenitors that undergo very complex patterns of dispersion.

In what it concerns this review we will consider those GABAergic neurons characterized by their content in calcium-binding proteins and electrophysiological properties: parvalbumin (PV) cells are fast-spiking interneurons with the morphology of chandelier and large basket cells, and calbindin (CB) cells are non-fast-spiking interneurons with the double-bouquet cells morphology [29,30].

The purpose of this article is to review and explore the cartography of this brain region: i) at the molecular level by summarizing our own recent data and that of others on the cellular localization of 5-HT_{1A} and 5-HT_{2A} receptors in primate and rodent brain PFC and ii) at the level of circuitries and projections, focused in rat PFC 5-HT_{2A} receptor-containing cells projecting to raphe nuclei (serotonergic cells), to ventral tegmental area, VTA (dopaminergic cells) and to accumbens nucleus.

BRAIN MAPS: MOLECULAR LEVEL

Cartography of 5-HT_{1A} receptors in prefrontal cortex

5-HT_{1A} receptors are negatively coupled to adenylyl cyclase through the $G_{i/o}$ protein inhibiting cAMP formation and function as inhibitory presynaptic and postsynaptic receptors. The early development of a selective agonist for 5-HT_{1A} receptors, 8-OH-DPAT [31] and the synthesis of its radioactive form [32] rapidly advanced the knowledge about the pharmacology and functionality of these receptors. 5-HT_{1A} receptor was the first serotonin receptor cloned and sequenced by sequence homology to adrenergic β2 receptor [33].

5-HT_{1A} receptor distribution in mammalian CNS was extensively studied first by receptor autoradiography using radiolabeled agonists ([^{3}H]-5-HT and [^{3}H]- 8-OH-DPAT)and found in high densities in the PFC in many species [34,35]. The antagonist molecule [^{3}H]-WAY 100635 selectively labels 5-HT_{1A} receptors by receptor autoradiography in human and monkey brain [36,37] and the derivative [*Carbonyl*-^{11}C]-WAY 100635 has been successfully used for *in vivo* labeling by PET in the same species [38-40] with comparable results.

The 5-HT_{1A} receptor mRNA distribution is very similar to that of the radiolabeled binding sites [36,41,42] indicating a primarily somatodendritic distribution. 5-HT_{1A} receptors are densely expressed in several brain areas, such as hippocampus, septum and raphe nuclei. In the raphe nuclei 5-HT_{1A} receptors are almost exclusively expressed in serotonergic neurons, as autoreceptor.

5-HT_{1A} receptor immunoreactivity and mRNA have been located in external PFC layers in rat [41,43-45] and in monkey and human [36,42,46-50].

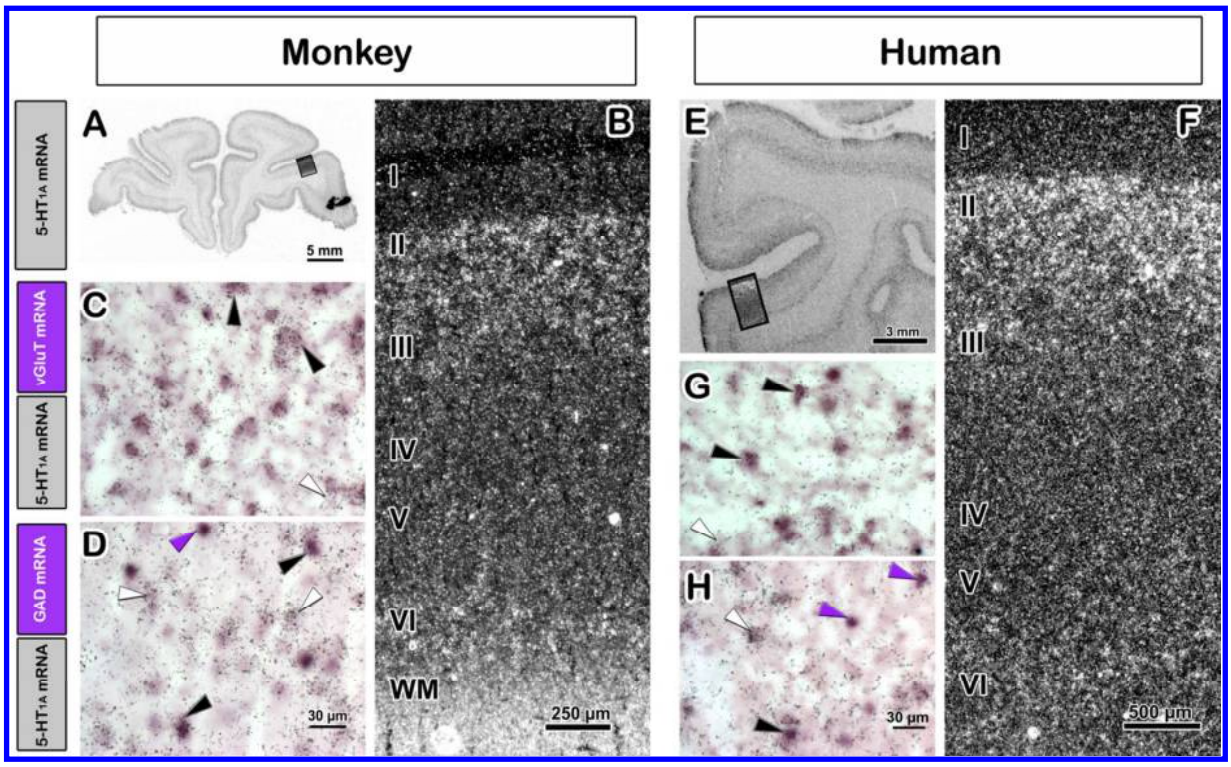

Figure 1. 5-HT_{1A} receptor mRNA in cortical layers and cell populations in monkey and human prefrontal cortex. Film autoradiographic image of a coronal section of monkey (A) and human (E) prefrontal cortex. The small rectangle in both dark-field microscopy pictures is shown at higher magnification in B and F of emulsion dipped hybridized sections (emulsion silver grains appear as bright white spots), with the six layers of the cortex numbered I to VI, from pial surface to white matter. C and G are high-magnification bright-field microphotographs of layer II from monkey and human hybridized, emulsion-dipped sections, showing simultaneously 5-HT_{1A} mRNA labeled with ^{33}P (clusters of dark silver grains) and vGluT1 mRNA (glutamatergic cells) identified as dark precipitate. D and H show the presence of 5-HT_{1A} mRNA and of GAD65/67 (GABAergic cells) also in layer II. The white arrow-heads point to radioactively labeled 5-HT_{1A} mRNA cell profiles, purple arrow-heads point to GABAergic cells labeled with digoxygenin, and black arrow-heads to double-labeled cells.

5-HT_{1A} receptor mRNA laminar distribution in monkey and human PFC, shown in Figure 1, is very similar for both species. The receptors are expressed abundantly in layer II-upper III which coincides well with the localization of these receptors by receptor autoradiography [35]. There is a lower expression in III-V layers and moderate in layer VI. In contrast, the laminar localization of 5-HT_{1A} receptor mRNA in rat PFC [41,43] is quite different: mainly located in deeper cellular layers (layer VI). The majority of glutamatergic cells of the external PFC layer II-upper III and about 50% of those in layer VI contain 5-HT_{1A} receptor mRNA in both human and monkey brain [50] (Table I). These receptors are also expressed in rat, monkey and human GABAergic PFC neurons at a lower percentage, around 20%, see Table I [43,50].

In monkey PFC 5-HT_{1A} receptors are expressed in 40% of the calbindin cells in layers II-upper III and in a few parvalbumin -containing interneurons [51], see Table I. Thus, this receptor is preferentially present in GABAergic interneurons innervating distal dendritic shafts and spines of pyramidal cells suggesting that it could be playing a role in the modulation of the cortical-serotonergic projection activity.

Cartography of 5-HT$_{2A}$ receptors in prefrontal cortex

5-HT$_{2A}$ receptor was initially described by radioligand binding assays with rat brain cortical membranes [52], back then known simply as 5-HT$_2$ receptors. They were cloned by homology with 5-HT$_{2C}$ receptors from human and rat brain [53,54]. 5-HT$_{2A}$ receptors are coupled to activation of protein kinase C via G proteins of the G_q/G_{11} family.

5-HT enhances spontaneous glutamate-mediated synaptic transmission onto pyramidal cells of layer V [55-57]. In rat brain the activation of 5-HT$_{2A}$ receptors in GABAergic interneurons inhibits pyramidal neurons [58,59]. *In vivo* physiological activation of 5-HT$_{2A}$ receptors excites pyramidal neurons in the medial PFC [60,61].

5-HT$_{2A}$ receptor anatomic distribution has been established in rat, monkey and human prefrontal cortex (and other brain areas) by several techniques, such as the most classic technique of receptor autoradiography, *in situ* hybridization histochemistry and immunohistochemistry [36,47,62-70]. These three approaches identify, respectively, location of the receptor binding sites, cells where mRNA is present, and receptor immunoreactivity location.

5-HT$_{2A}$ receptor mRNA laminar distribution in monkey and human PFC, as shown in Figure 2, is very similar for both species. The mRNA for this receptor is abundant in layers II-V of monkey and human PFC [71], which is compatible with data obtained by receptor autoradiography using [^{3}H]MDL100907 [66,68] and [^{3}H]ketanserine [63,72-74] being layers II and IV the most enriched in 5-HT$_{2A}$ receptor binding sites.

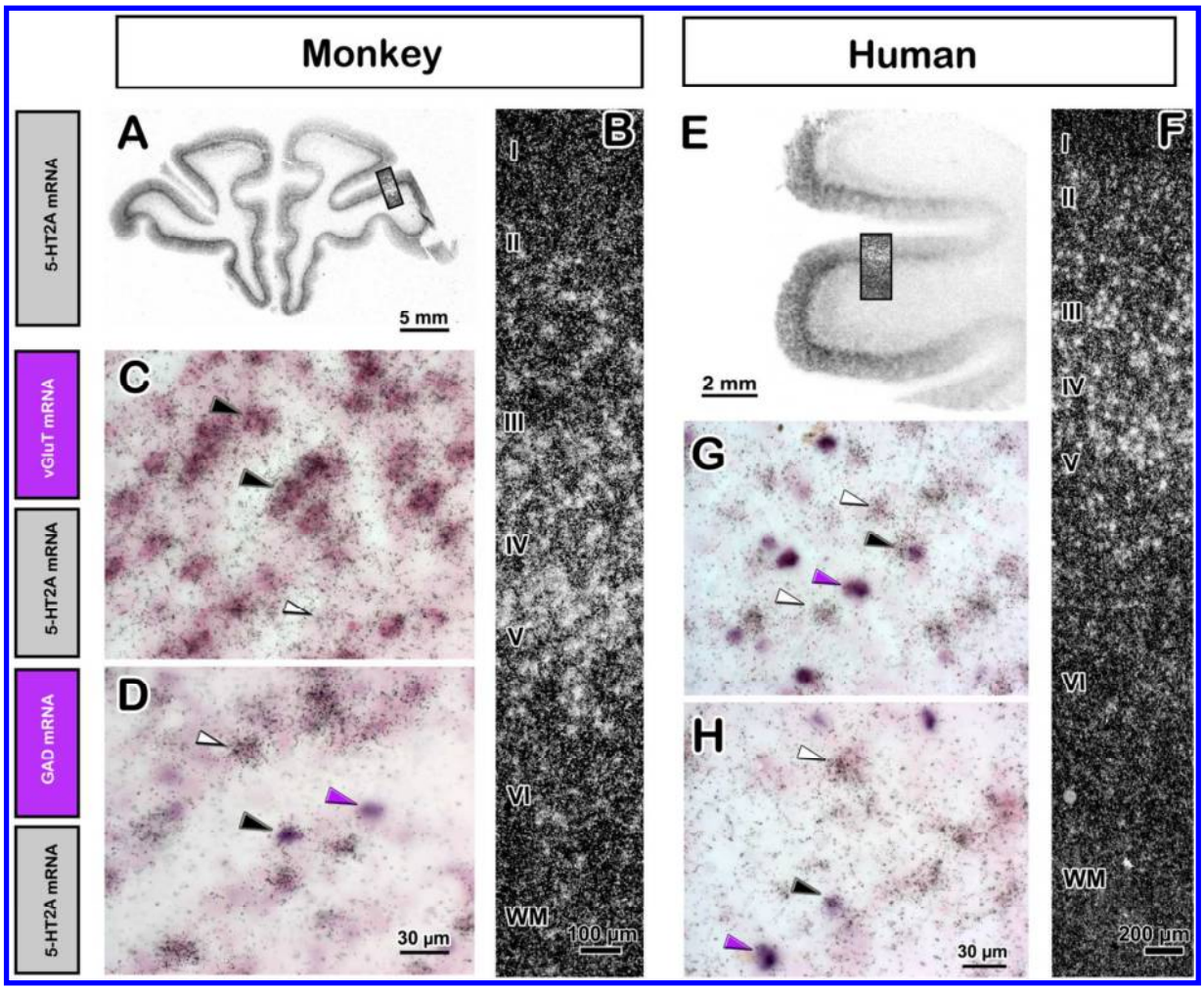

Figure 2. 5-HT$_{2A}$ receptor mRNA in cortical layers and cell populations in monkey and human prefrontal cortex. Film autoradiographic image of a coronal section of monkey (A) and human (E) prefrontal cortex. The small rectangle in both dark-field microscopy pictures is shown at higher magnification in B and F of emulsion dipped hybridized sections (emulsion silver grains appear as bright white spots), with the six layers of the cortex numbered I to VI, from pial surface to white matter. C and G are high-magnification bright-field microphotographs of layer II from monkey and human hybridized, emulsion-dipped sections, showing simultaneously 5-HT$_{2A}$ mRNA labeled with ^{33}P (clusters of dark silver grains) and vGluT1 mRNA (glutamatergic cells) identified as dark precipitate. D and H show the presence of 5-HT$_{2A}$ mRNA and of GAD65/67 (GABAergic cells) also in layer II. The white arrow-heads point to radioactively labeled 5-HT$_{2A}$ mRNA cell profiles, purple arrow-heads point to either glutamatergic or GABAergic cells labeled with digoxygenin, and black arrow-heads to double-labeled cells.

We have provided quantitative information on the type of cells expressing these receptors in monkey and human PFC [71] as well as in rat PFC [43]. The majority (98-100 %) of the monkey and human PFC cells expressing 5-HT$_{2A}$ receptor mRNA in layers III and V are glutamatergic pyramidal neurons (see Table I). This number is lower in the case of the rat PFC, ranging from 55-80%. In contrast, 5-HT$_{2A}$ receptor mRNA expression in GABAergic cells in those cortical layers is consistently lower for the three species (16-25 %) (Table I). In terms of cell percentages, the expression of 5-HT$_{2A}$ receptor mRNA in PFC glutamatergic and GABAergic cell populations in human and monkey is similar to that reported in the rat PFC by *in situ* hybridization histochemistry [43] and by immunohistochemistry [75].

In monkey and human brain the presence of these receptors in the GABAergic cell population was also quantified in CB and PV neurons (Table I). 5-HT$_{2A}$ receptors are differentially expressed in the GABAergic

interneurons: 50 to 69% in PV neurons and a higher proportion, 61-87% in the CB cell population in both species expressed 5-HT_{2A} receptor mRNA.

Receptor	Glutamatergic		GABAergic		Calbindin	Parvalbumin
5-HT1A	**Layer II**	**Layer VI**	**Layer II**	**Layer VI**	**Layer II-III / Layer VI**	**Layer II-III / Layer VI**
Human	80%	50%	20%	20%		
Monkey	80%	50%	20%	20%	43% / 15%	7% / 6%
Rat	60%	50%	25%	25%		
5-HT2A	**Layers II-V**	**Layer VI**	**Layers II-V**	**Layer VI**	**Layer III / Layer V / Layer VI**	**Layer III / Layer V / Layer VI**
Human	95%	75%	16%	16%	87% / 80% / 61%	45% / 63% / 52%
Monkey	95%	60%	20%	35%	75% / 61% / 63%	58% / 69% / 48%
Rat	55-80%	30%	25%	10%		

Table I: **5-HT_{1A} and 5-HT_{2A} receptor mRNA expression in glutamatergic and GABAergic cells.** Data are taken from de Almeida and Mengod previous publications [50,71] and represent the percentage of cells of a given phenotype that express 5-HT1A or 5-HT2A receptors in the different PFC layers.

The basic cell composition of the PFC is schematized in figure 3, where the main results concerning the distribution of 5-HT_{1A} and 5-HT_{2A} receptors mRNA in pyramidal and GABAergic neurons of the PFC as we have discussed above are summarized.

The presence of 5-HT_{2A} receptors in the two main populations of neurons in PFC, suggests that the effect of the increment in extracellular GABA levels produced by activation of these receptors [76] could be due direct action on GABAergic neurons or indirectly through activation of pyramidal cell collaterals.

5-HT_{2A} receptors are expressed at a notable percentage in PV interneurons (basket and chandelier) known to produce a prominent perisomatic inhibition (Figure 3) of the pyramidal cells via innervation at the soma, axon initial segments or dendritic shafts close to the soma, supporting the idea that 5-HT can suppress pyramidal firing by activating the 5-HT_{2A} – containing perisomatic inhibitory neurons.

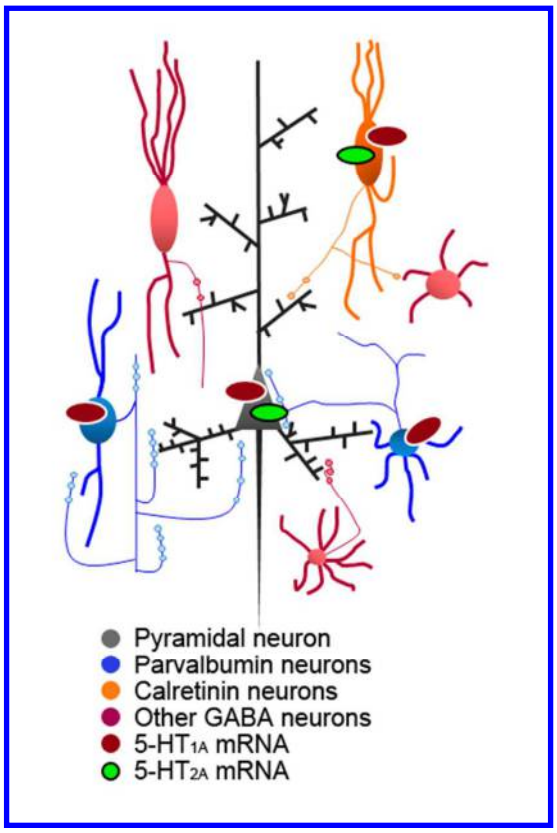

Figure 3. Schematic summary of cytoarchitecture of the prefrontal cortical cells expressing 5-HT_{1A} and 5-HT_{2A} mRNA. A typical PFC pyramidal neuron (grey) could be expressing either 5-HT_{1A} (red dot) or 5-HT_{2A} (green dot) or both receptors receives inhibitory synaptic inputs by different morphological classes of intrinsic GABAergic neurons: chandelier and wide arbor parvalbumin cells (blue) expressing 5-HT_{1A} receptor mRNA, and the double bouquet calretinin cells (orange) that could express either 5-HT_{1A} or 5-HT_{2A} receptor mRNA.

BRAIN MAPS: CIRCUITRIES AND PROJECTIONS

5-HT2A receptors in identified projection neurons of the prefrontal cortex

The PFC is highly interconnected with other brain areas. In addition to crucial information provided by electrophysiological studies, tract tracing techniques in combination with immunohistochemistry have been particularly useful to explore the connectivity of the PFC. Furthermore, in some cases, the use of electron microscopy has allowed the precise identification of synaptic contacts of PFC terminal afferents and efferents with different cell types [77-80]. It is well established that the PFC projects to and receives inputs from monoaminergic cell groups in the hypothalamus and brainstem, and can thus exert a control on these neurotransmitter systems that modulate most brain regions. We have been particularly interested on the connections of the PFC with the dorsal raphe nucleus (DR), where most ascending serotonergic neurons are located, and also with the VTA dopaminergic neurons because of the involvement of these brain centers in affective and psychiatric disorders. The interactions between the PFC, the DR and the VTA are likely involved in the mechanisms underlying the therapeutic action of antidepressants and antipsychotic drugs. Because of the relevance of serotonergic receptors as targets of antipsychotic drugs, in particular of atypical antipsychotics, it has been our interest to determine whether 5-HT receptor subtypes are present in PFC cells that project to the DR and to the VTA. The combination of tract tracing and *in situ* hybridization histochemistry techniques has allowed the visualization of 5-HT_{2A} receptor mRNA in identified populations of PFC pyramidal neurons in the rat brain [81,82].

As shown in Figure 4A,B, the microiontophoretic application of retrograde tracers such as cholera toxin subunit B (CTB) or fluorogold (FG) into the rat DR nucleus results in the labeling of cell bodies, presumably belonging to layer V pyramidal neurons, in the mPFC (mainly prelimbic and anterior cingulate areas, but also in the infralimbic cortex), and in the lateral orbitofrontal cortex, extending to the adjacent ventral orbitofrontal and ventral insular agranular cortical areas [17,82-84]. Such retrogradely labeled DR-projecting cells are found in both brain hemispheres. As determined by *in situ* hybridization histochemistry, a high proportion of these neurons present 5-HT_{2A} receptor mRNA, accounting for around 65 % in the mPFC (Figure 5A1) and 75 % in the orbitofrontal cortex [81].

PFC projection neurons that innervate the rat VTA (Figure 4C,D) are also located along layer V of the medial PFC, including all its subregions, and also in orbitofrontal cortex in particular in its the ventral part [82,84]. In contrast to the DR, PFC projections to VTA are found almost exclusively in the hemisphere ipsilateral to the tracer injection side. The concomitant use of different retrograde tract tracers applied into the DR and the VTA has allowed the identification of a substantial number of mPFC cells that simultaneously project to both monoaminergic nuclei [82]. This observation supports previous electrophysiological data suggesting that PFC efferents send branching axons to DR and VTA [60], as has been demonstrated for other PFC neurons that send dual projections to other brain regions [85]. Concerning the presence of 5-HT_{2A} receptor mRNA, it has been detected in more than 50 % of mPFC (Fig. 5B) and in almost 60 % of orbitofrontal cortex pyramidal neurons that project to VTA [81]. The existence of 5-HT_{2A} receptor in mPFC DR/VTA-projecting neurons remains to be fully determined.

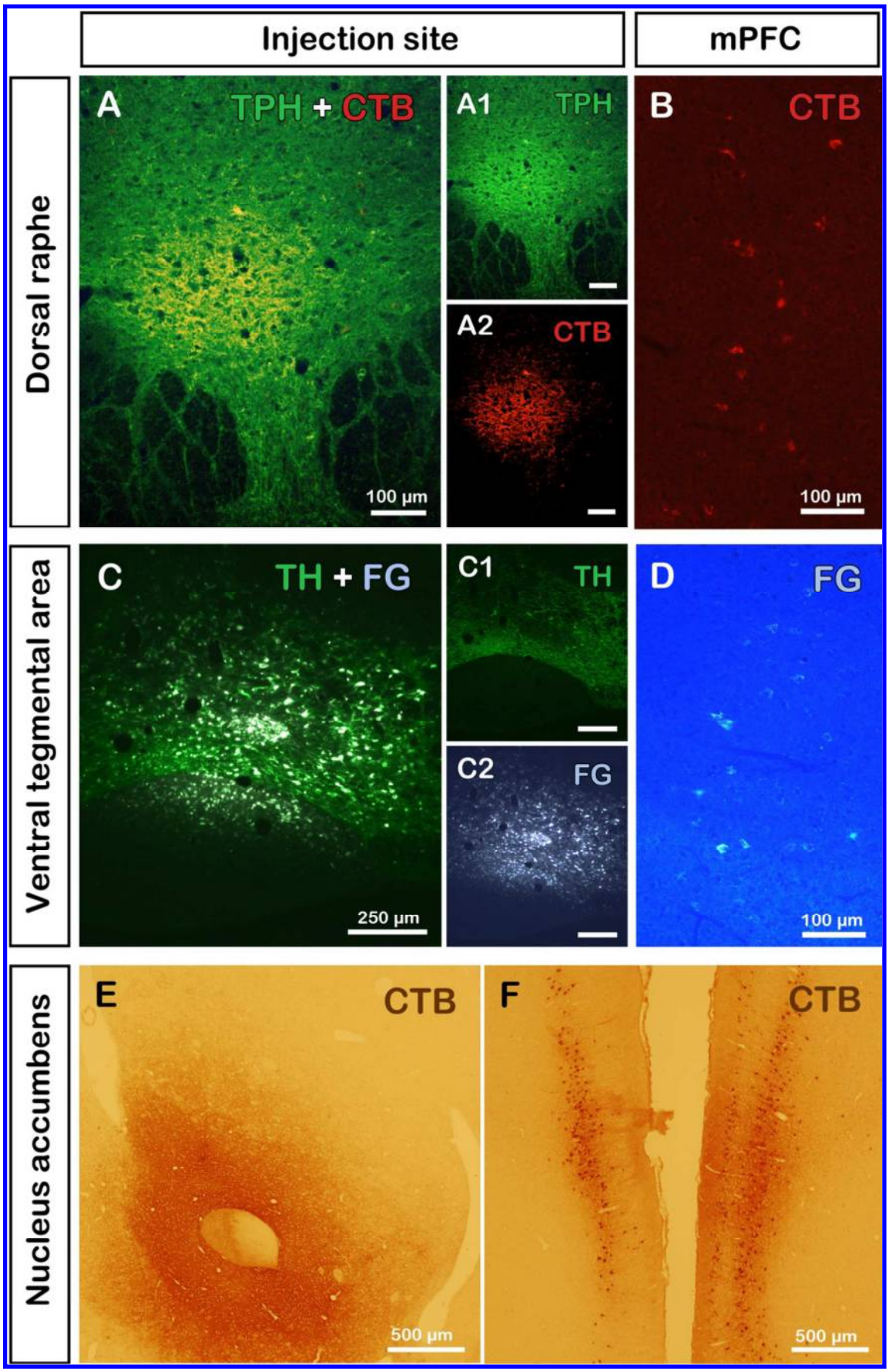
Injection site
mPFC
Dorsal raphe
A
TPH + CTB
100 µm
A1
TPH
A2
CTB
B
CTB
100 µm
Ventral tegmental area
C
TH + FG
250 µm
C1
TH
C2
FG
D
FG
100 µm
Nucleus accumbens
E
CTB
500 µm
F
CTB
500 µm

Figure 4. Identification of medial prefrontal cortex projection neurons. Microphotographs show the injection sites of the tract tracers cholera toxin subunit B (CTB) or fluorogold (FG) into the dorsal raphe (A), ventral tegmental area (C) and nucleus accumbens (E) and the corresponding retrogradely labeled neurons in the medial prefrontal cortex (B,D,F). The correct placement of the tracers in the dorsal raphe and ventral tegmental area is verified by staining of tryptophan hydroxylase (TPH) (A,A1) and tyrosine hydroxylase (TH) (C, C1), respectively. In these regions both enzymes and CTB (A,A2) are detected by indirect immunofluorescence, while FG (C,C2) is visualized by its own fluorescence. The injection site of CTB in the nucleus accumbens (E) is visualized by indirect ABC-immunoperoxidase with DAB as substrate (brown precipitate). In the medial prefrontal cortex, retrogradely transported tracers from the dorsal raphe (B), ventral tegmental area (D) and nucleus accumbens (F) are found in neurons along layer V and outer layer VI ipsilateral to the injection side. Labeling in the contralateral layers V and outer VI is also observed after tracer application in the dorsal raphe (not shown) and nucleus accumbens. Nucleus accumbens-projecting cells are also found in the ipsilateral layer II. See procedures in [81,86].

We have also explored whether cortical 5-HT_{2A} receptors might control the function of the nucleus accumbens, which receives strong innervation from the mPFC [84] and also inputs from the VTA [77]. Retrograde tracer injections into the rat nucleus accumbens (Fig. 4E) result in the labeling of numerous neuronal cell bodies in the mPFC located mainly in the prelimbic region, but also ventrally in the infralimbic and dorsally in the anterior cingulate cortical areas (Fig. 4F) [84,86-88]. In these three mPFC regions, labeled neurons are found along layer V extending to VI in both hemispheres, and also in layer II and outer layer III of the hemisphere ipsilateral to the tracer injection site. Among retrogradely labeled cell bodies of mPFC neurons projecting to the nucleus accumbens, around 43 % show expression of 5-HT_{2A} receptor mRNA, with small variations between layers and cortical regions [86]. These data suggest that the mechanism of action of atypical antipsychotics, besides the inhibition of D2 receptors in the nucleus accumbens, also involve a reduction of the glutamatergic activity in this area through the blockade of 5-HT_{2A} receptors in mPCF afferents.

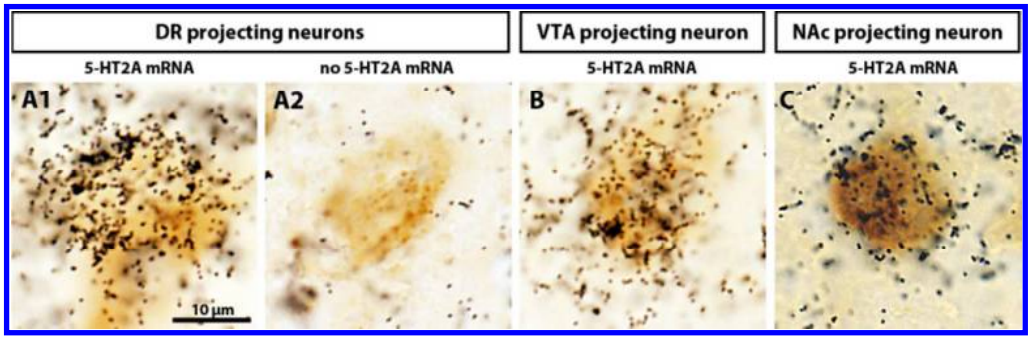

Figure 5. Expression of 5-HT_{2A} receptor mRNA in rat medial prefrontal cortex projection neurons. Microphotographs show mPFC cells retrogradely labeled after cholera toxin B subunit injection into the dorsal raphe nucleus (A1, A2) or ventral tegmental area (B) or fluorogold injection into the nucleus accumbens (C). Both retrograde tracers were detected by indirect ABC-immunoperoxidase staining with DAB as substrate (brown precipitate). The presence of 5-HT_{2A} receptor mRNA (black grains) was demonstrated *in situ* hybridization histochemistry using simultaneously 3 different, specific oligonucleotide probes 3'-end labeled with ^{33}P-dATP and autoradiographic detection with nuclear track emulsion. Double-labeling is shown in cells that project to the dorsal raphe (A1), ventral tegmental area (B) and nucleus accumbens (C). Panel A2 illustrates a neuron retrogradely labeled from the dorsal raphe which does not contain 5-HT_{2A} receptor mRNA hybridization signal. See procedures in [81,86].

A graphic summary of these data is shown in Figure 6. Altogether these observations demonstrate that in the rat PFC 5-HT_{2A} receptors are expressed in pyramidal tract neurons that project to DR, VTA and nucleus accumbens, and also in intratelencephalic neurons of layer L2/3 projecting to the latter, according to Shepherd's nomenclature of neocortical excitatory cells [22].

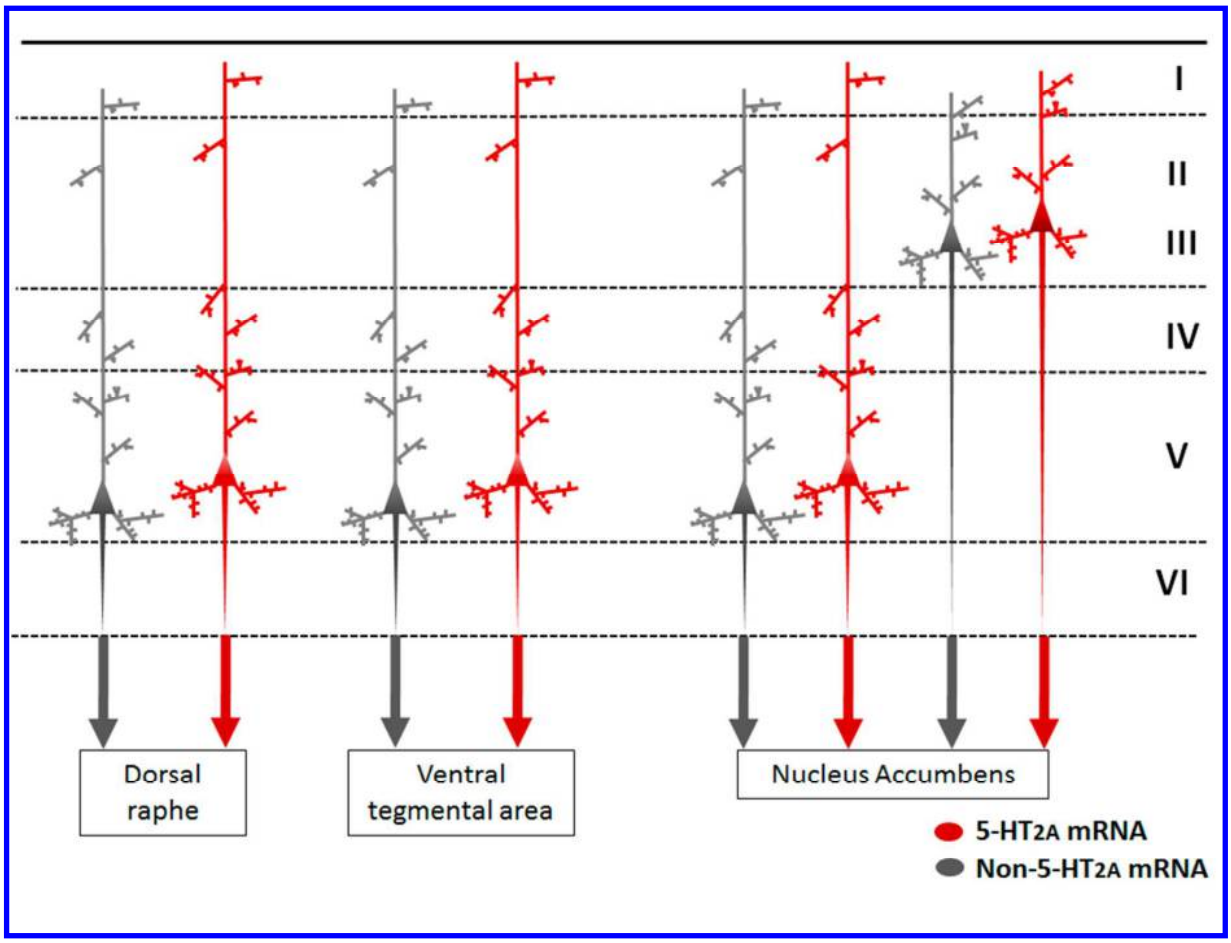

Figure 6. Schematic summary of the prefrontal cortical cell projections expressing 5-HT_{2A} mRNA.

CONCLUSIONS

The cartography of the 5-HT_{1A} and 5-HT_{2A} receptor mRNAs in the PFC of rat, monkey and human has been established by different neuroanatomical techniques. The distribution for these two receptors is quite similar in human and primates, with a clear lamination of the receptor expressing cells. In contrast, in the rat these receptors and their mRNAs are more homogeneously distributed among the different layers. However it should be mentioned that in rat PFC, DR-, VTA- and nucleus accumbens-projecting cells, some of which express 5-HT_{2A} receptors, are arranged in well-defined layers.

The cortical microcircuitry is integrated by pyramidal neurons and GABAergic interneurons. Given that 5-HT_{2A} receptor-expressing neurons in prefrontal cortex project to the serotonergic raphe nuclei, and the existence of raphe-cortical projections, serotonin can modulate the activity of these prefrontal cortex microcircuits and circuits through the direct inputs into both pyramidal neurons and GABAergic interneurons via the 5-HT_{2A} receptors expressed by these neurons.

In addition, data on the presence of 5-HT_{2A} receptor mRNA in PFC neurons that project to VTA or to nucleus accumbens in the rat are relevant for the understanding of the mechanism of action of atypical antipsychotic drugs.

On the other hand, 5-HT_{1A} receptors located in the PFC are also sites of action of atypical antipsychotics. The effects of these drugs on PFC 5-HT_{1A} receptors have been shown to distally activate the mesocortical pathway, increasing local dopamine release. This effect would be involved in the amelioration of cognitive deficits and negative symptoms in schizophrenia and other psychotic disorders.

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Author contributions

All authors designed the review, wrote it, and contributed to literature search. GM and RC designed and created the figures.

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Notes

The authors declare no competing financial interest.

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Graphic abstract