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HTR1B as a risk profile maker in psychiatric disorders: a review through motivation and memory

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Abstract

Purpose Serotonin receptor 1B (HTR1B) is involved in the regulation of the serotonin system, playing different roles in specific areas of the brain. We review the characteristics of the gene coding for HTR1B, its product and the functional role of HTR1B in the neural networks involved in motivation and memory; the central role played by HTR1B in these functions is thoroughly depicted and show HTR1B to be a candidate modulator of the mnemonic and motivationally related symptoms in psychiatric illnesses.

Methods In order to challenge this assessment, we analyze how and how much the genetic variations located in the gene that codes for HTR1B impacts on the psychiatric phenotypes by reviewing the literature on this topic.

Results We gathered partial evidence arising from genetic association studies, which suggests that HTR1B plays a relevant role in substance-related and obsessive compulsive disorders. On the other hand, no solid evidence for other psychiatric disorders was found. This finding is quite striking because of the heavy impairment of motivation and of mnemonic-related functions (for example, recall bias) that characterize major psychiatric disorders.

Conclusions The possible reasons for the contrast between the prime relevance of HTR1B in regulating memory and motivation and the limited evidence brought by genetic association studies in humans are discussed, and some suggestions for possible future directions are provided.

Keywords Memory · Motivation · Receptor · Serotonin · 5-HT1B · Gene · Single nucleotide polymorphism · Psychotic disorder · Bipolar disorder · Obsessive-compulsive disorder · Substance-related disorders · Suicide

Introduction

The serotonin system regulates a wide spectrum of neuronal activities, with its influence reverberating into physiological events as diverse as body temperature, mood level, hormone release, food intake, sleep balance and learning abilities. This relevance is based upon a vast network of serotonergic connections that reach virtually the whole central nervous system and are orchestrated by the activities of at least 14 known distinct serotonin receptors. The detailed knowledge of the characteristics of the serotonin receptors will hopefully shed some light on the mechanisms that underlie psychiatric disorders. Based on this rationale, a wide range of genetic investigations have been performed so far that could nevertheless still not produce conclusive results. The unraveling of the reasons for this incomplete result is a relevant topic in contemporary scientific debate. Starting from this perspective, we here retrace the reasons why one of these receptors, HTR1B, can be considered a good candidate to be a putative regulator of psychiatric disorders, and we compare this set of evidence with the results brought by the genetic association studies focused on HTR1B mutations. Collecting the first set of evidence, motivation and memory functions in animal models were chosen as relevant points in the analysis of HTR1B functional relevance, because:

1. Memory and motivation are high brain functions impaired in many psychiatric phenotypes.
2. Animal models allow a refined experimental modulation of HTR1B activities and there are animal tests that are considered to be good models for these functions in humans.

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The limits and advantages of this translational approach are critically discussed. The results of the genetic association analyses are then reported and discussed. The inconsistency between the relevant role of HTR1B and the genetic association results are discussed.

Materials and methods

Information on the HTR1B as a gene and as a receptor, and on the associations between the genetic variations and the protein functions is drawn from international databases (www.geneontology.org; www.genecards.org; www.ensembl.org; www.pdb.org; <http://www.ncbi.nlm.nih.gov/>).

The first part of the paper is a reasoned review of the evidence on motivation and memory as products of the functions of specific neural networks. Then, the functional impact of HTR1B on these dimensions is depicted. For this part of the review, we searched the literature in April 2009 using the following databases: PubMed, EMBASE, International Pharmaceutical Abstracts (IPA) and Web of Science. These were searched using the following items: “HTR1B,” “serotonin receptor 1b,” “5-HT1B,” “agonist,” “antagonist,” “animal model,” “mice” and “mouse” in combination. The same databases were searched for the second part of the review, which focuses on the genetic association studies. The following terms were searched for: “HTR1B,” “serotonin receptor 1b,” “5-HT1B,” “depressive disorder,” “anxiety disorder,” “schizophrenia,” “psychotic disorder,” “eating disorder,” “suicide behaviour,” “obsessive compulsive disorder,” “substance related disorder,” “dependence,” “abstinence,” “genetic variation,” “SNP” and “polymorphism,” and “genetic variation” in combination.

HTR1B as a gene

The HTR1B gene is located on chromosome 6 at position 78,228,641–78,229,900 (http://www.ensembl.org/Homo_sapiens/index.html). It contains one exon and codes for a 1,260 bps transcript. The gene’s transcript produces one product with no known isoforms. Table 1 reports the most relevant variation within the exon sequence of HTR1B along with their frequencies on the HapMap populations. Only eight exonic variations are listed in Table 1 that are nevertheless of prime relevance for further investigations into this gene in that they directly change the amino-acidic sequence of the receptor, thus causing variations in its 3D structure, which is tightly associated with its functions. Thus, further investigations should include those variations in their analysis. Nevertheless, intronic variations may be relevant as well in that they are able to change the regulatory profile of the gene, thus impacting on the

receptor’s density on the surface of the cells. Table 2 lists the entire sequence of the gene and highlights the most relevant variations. Figure 1 shows some of the most relevant coding mutations and their location near to, or within, the genetic frame that code for putative functional enzymatic sites. The number of validated variations localized in the HTR1B is 44. The number of tagging variations in the CEU AND YRI populations is 1 (rs6298), rs6296 is a tagging variation in the CHB and JPT populations. Of note, rs6298, rs130060 and rs6296 are characterized by a relevant frequency in the general population. They give rise to changes in positions 43, 124 and 287 respectively. Substitution in position 124 is non-synonymous and it leads to a Cys to Phe change, corresponding to alleles G and T respectively. Both amino-acids are non-polar and have a similar hydrophathy index (2.5 and 2.8 respectively). The precise role of this mutation is awaiting definition. Four variations can tag HTR1B in the CEU population: rs11568817, rs6298, rs4140535 and rs130058. Other relevant mutations are the Phe219Leu, Ile367Val and Glu374Lys; these could potentially affect ligand binding or interaction with G proteins [143]. The majority of these variations were not investigated in psychiatric disorders (Tables 3, 4, 5, 6, 7). Finally, HTR1D, HTR1E and HTR1F are known as the paralogs of HTR1B, that is, genes that are related by duplication to HTR1B, but have evolved different functions.

Possible relevance of HTR1B mutations in the pharmacodynamics of antidepressant and antipsychotic drugs

The genetic variations of HTR1B can result in events related to the pharmacodynamics of antidepressant or antipsychotic events in different ways:

1. A mutation that changes the amino-acidic sequence of the receptor can determine an altered enzymatic function, either because located in the enzymatic active site of the receptor, or because able to change the 3D structure of the receptor, thus interfering with its function.
2. A mutation located in the regulatory sites of the gene can change its expression rate, thus causing a variation in the density of the receptor on the surface of neurons, with consequences for the dynamics of drugs that directly or indirectly act on the HTR1B coded protein.

It has been demonstrated that the second extracellular loop and the fifth transmembrane domain of the HTR1B receptor is necessary to and sufficient for the binding function of the HTR1B receptor [183]. Thus, variations occurring in parts of the gene that code for these amino-acidic sequences are candidate modulators of the functions

Table 1 HTR1B exonic variations and their frequencies at HapMap populations

Residue	SNP ID	SNP type	Alleles	CEU		HCB		JPT		YRI	
				1	2	1	2	1	2	1	2
43	rs6298	Synonymous	C/T	0.66	0.34	0.467	0.533	0.433	0.567	0.758	0.242
92	rs130059	Synonymous	A/G	No data*	No data						
124	rs130060	Non-synonymous	G/T	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
219	rs130061	Non-synonymous	C/T	0.00	1.00	0.00	1.00	0.01	0.99	0.00	1.00
235	rs130062	Synonymous	C/T	No data**	No data						
287	rs6296	Synonymous	C/G	0.34	0.66	0.54	0.46	0.57	0.43	0.24	0.76
367	rs130063	Non-synonymous	A/G	1.00	0.00	0.97	0.03	0.99	0.01	1.00	0.00
374	rs130064	Non-synonymous	C/T	0.00	1.00	0.01	0.99	0.00	1.00	0.00	1.00

1 Allele 1 is the first allele that is reported in the column “alleles,” for example, allele 1 at rs6298 is C

2 Variations with interesting frequencies in the populations are in bold

There is inconsistent reporting with regard to allele types from NCBI to Ensembl. NCBI data are reported

*Populations other than the HapMap population report a higher frequency for the G allele

**Populations other than the HapMap population report a higher frequency for the C allele

of the receptor. Moreover, events related to the regulation of the expression rate of HTR1B are closely associated with the antidepressant effect of the pharmaco-treatment of depression; paroxetine and fluoxetine determine a down-regulation of the HTR1B mRNA expression in the serotonergic neurons whose cell bodies are located in the dorsal raphe nucleus in mice [3], an event that is thought to be directly correlated with the antidepressant efficacy of these drugs [156]. Consequently, a mutation located in the regulatory regions of the HTR1B may be able to enhance or dampen the effects of these drugs, by the way of a genetically determined increased or decreased flexibility in the regulation of the genetic expression rates, which are the targets of the antidepressant treatments. Nevertheless, the mechanisms of antidepressant action are likely much more complicated. For example, in a recent study conducted by Orsetti and colleagues [114], the antidepressant activity of the second generation antipsychotic quetiapine was associated with an altered expression pattern of a list of 11 genes (namely: *tgf2*, *Gad1*, *Plcb1*, *Camk2a*, *Homer1*, *Senp2*, *Junb*, *Nfib*, *Hes5*, *Capon*, and *Marcks*) in the frontal cortex of mice. These genes code for proteins involved in second messenger activities or act as regulators of transcriptional events. Notably, none of the receptors of the serotonin system is present, even though the serotonin regulation could be indirectly associated with the activity of these proteins. Moreover, it must be underlined that these effects have been identified in the prefrontal cortex, whilst the raphe nucleus has not been investigated by Orsetti and colleagues. This may explain the different result attained by Anthony et al. [3] and Orsetti et al. [114], and may suggest that the brain might react to the antidepressant treatment in ways that are highly specific with respect to the brain area under analysis.

HTR1B as a protein

HTR1B is 390 amino-acids long and it weighs 43,568 Da. As an active enzyme it is located within the cellular membrane and it belongs to the super-family of the multi-pass membrane proteins. The 3D model is shown in Fig. 1; the active parts of the protein are highlighted and correlated with the coding mutations that characterize the gene. HTR1B functionally couples with a $G_{1/0}$ protein, the activation of which results in two main metabolic events: a decreased level of cAMP (cyclic AMP), and the inhibition of the RAP1 guanine nucleotide exchange factor (Rap1GAP) activity.

A HTR1B-driven decreased level of cAMP

A decreased intracellular concentration of cAMP drives a diminished activation of the protein kinase A, a group of serine/threonine protein kinases that catalyze the reaction $\ll \text{ATP} + \text{a protein} = \text{ADP} + \text{a phosphoprotein} \gg$ upon a set of cytosolic and nuclear protein products. The phosphorylation of a protein drives its activity profile; the refined orchestration of the PKA-dependent phosphorylation events upon key enzymatic factors decide a cell's fate by regulating transcription [79, 140], metabolism [47], cell cycle progression [103, 152], and apoptosis [19, 44].

A HTR1B-driven inhibition of the Rap1GAP activity

RAP1GAP activates the RAP1, a member of the Ras family of small GTPases, and favors switching to the RAP1 state, which hydrolyzes GTP to GDP [68]. This reaction can be reversed by the GEF (guanine nucleotide exchange factors)

Table 2 HTR1B sequence and most relevant variations (Ensembl database)

Number of base	Bases and mutated bases	Corresponding mutation	Corresponding SNP
1	AGCTCGTCCGAGTGGCCAGAGAGTGAAGAGAGAGGGAGGGCAGAGCTCCGGCCGAG <u>R</u> CG	58:G/A;	RS11965950
61	CGGCGCAGCGTCTCTTAGACTTACCCACCAGCTCTGGCGCCGCTGCAGCCCCC		
121	AAAAGTGGCCAGCTTGGGGCGAGGGTGG <u>K</u> AATGCAAGATCTCGGGACCTCTCGCTGGC	151:G/T;	rs130056
181	CTGCAAGCTTTGGTCTCTACACCTAGGAACTCCTGTGGCAAAGTCTGCAGATCCAAA		
241	GCGTCCAGGTTAGGAGACGCTCAGCCTCAAGCAACTGGGGTAAGAGATCCCATTTGGTCA		
301	CGGAGCAGGGCTCGTGGGGCAGCTCTTAGCAACCAGG <u>K</u> C <u>K</u> AAGACCCGGTGTGGAGAG	400:T/G; 402:T/G;	rs11568817; rs11575885
421	GAACA <u>W</u> CCACAGACGCGCGCTTAGCTAGCGCTCTGGAAGTGCAGGGAGGGCCCGC <u>C</u>	426:A/T; 480:- /CC;	rs34311679; rs34401185
481	<u>C</u> TGCCTGGCTGCCGACCC <u>W</u> TGACCTCTAGTTTCAGCTGTGAACCTGGGCGGAGGAATA	501:A/T;	rs130058
541	ATTGAGGAATCAGCGAACTATCAACTGGGGACAAACCTGCGATCGCCACGGTCTCTCCG		
601	CCCTCTCTCTCGTC<u>R</u>CTCCATGCCAAGAGCTGCCTCCGGAGCTGGGGCGAGGAGAGC	616:G/A;	rs34514827
661	CATGGAGGAACCGGGTGTCTAGTGCCTCCACCGCCCGCGGGCTCCGAGACTGGGT		
721	TCCTCAAGCCAACTTATCTCTGCTCCCTCCAAAAGTGCAGCGCAAGGACTACATTTA		
781	CCAGGACTC<u>Y</u>ATCTCCCTACCCTGGAAAGTACTGCTGGTTATGCTATTGGCGCTCATCAC	790:C/T;	rs6298
841	CTTGGCCACCAGCTCTCCAATGCCTTTGTGATTGCCACAGTGTACCGGACCCGAAACT		
901	GCACACCCCGCTAACTACCTGATGCCTCTCTGGC<u>R</u>CTCAGCACCTGCTTGTGTCCAT	937:G/A;	rs130059
961	CCTGGTGTAGCCCATCAGCACCATGTACACTGTACCAGCGCTGGACTGGGCCAGGT		
1021	GGTCTGTGACT<u>K</u>CTGGCTGTGTCGGACATCACTTGTGCACTGCCTCCATCCTGCACCT	1032:T/G;	rs130060
1081	CTGTGTCATCGCCCTGACCGCTACTGGGCCATCACGGACCGCTGGAGTACTCAGTAA		
1141	AAGGACTCCCAAGAGGGCGGTCATGATCGCGTGGTGGGTCTTCTCCATCTCTAT		
1201	CTCGTGGCCCTTCTTCTGGCGTCAGGCTAAGCCGAAGAGAGTGTGGAATGCGT		
1261	GGTGAACACCACCACATCTCTACACGGTCTACTCCACGGTGGGTGCTTTCTAC<u>Y</u>TCCC	1316:T/C;	rs130061
1321	CACCTGTCTCTCATGCCCTCTATGGCCGATCTACGTAGAAGC<u>Y</u>CGCTCCCGGATTTT	1366:C/T;	rs130062
1381	GAAACAGACGCCCAACAGGACCGGCAAGCGCTTGACCCGAGCCAGCTGATAACCGACTC		
1441	CCCCGGGTCCACGTCTCGGTACCTCTATTAACCTCGGGTTCCCGACGTGCCAGCGA		
1501	ATCCGGATCTCCTGTGTATGT<u>S</u>AACCAAGTCAAAGTGCAGTCTCCGACGCCCTGCTGGA	1522:G/C;	rs6296 (cited in Pubmed at 17948897; 15206000)
1561	AAAGAAGAAACTCATGGCCCTAGGGAGCGCAAAGCCCAAGACCTTAGGGATCATTTT		
1621	GGGAGCCCTTATTGTGTGGCTACCTTCTTTCATCATCTCCCTAGTGTGCTATCTG		
1681	CAAAGATGCCTGTGTTCCACCTAGCCATCTTTGACTTCTTACATGGCTGGCTATCT		
1741	CAACTCCCTCATCAACCC<u>R</u>TAATCTATACCATGTCCAA<u>R</u>AGGACTTTAAACAAGCATT	1760:A/G; 1781:G/A;	rs130063; rs130064
1801	CCATAAACTGATACGTTTTAAGTGACAAGTTGACTTGC<u>R</u>TTTTCAGT<u>R</u>GGGTGCCTA	1841:G/A; 1850:G/A;	rs6297; rs3827804
1861	AGCGACCTTTGGGACCAAGTTGTCTCGTTCCACAGTAGGTGCAATCTCTTTTCGCG		
1921	GTTTCTGGTCCCAGCAGGCTCTCTCTCTGGGCAAGGGCAATGGATCCTGAGAAGCCA		
1981	GAATAGTCTGAGAGAGCTCTGAAAGGAGAAGTGTGAAACTAAATGTAGAGCTTCCC		
2041	TGCCAGGAGGAGGCTCACTTCTCCCTCAAGCCCGGGCTCAGCACTGACCCCTGCG <u>Y</u>	2100:C/T;	rs9361234;
2101	AGCCAATCCCAAAGGGGTTGCAACTTTTAAAAATTGATAATGGAAGGGAATCCCTGCC		
2161	TGCTTTGGTATCGTGGATAATGCCACTAGAAGCAGTGTACTTGTAAATGTTGTCTGAAG		
2221	CCTGCTGAGACAGATCTACATACGCTGGCAGTACTTGAAGTAGACGCTTAATGCCCT		
2281	GTGTTTT <u>GG</u> GGGGAGAACTTTGTGTACAGCTTAATTTAAGAACAGTACTTTGGCATC	2289:GG/-;	rs5813857
2341	ATTCACTCTTCACTTTTGTCTATTTAACTTGGTTGGAGAAACTTGTGATTGGTGTCT		
2401	TCAAACCTATGTGTGGCTTGGATGGCGCAGAGAAACCTTGAAGAGTTAACAGCAAATTT		

Underlined = location of SNP; bold = insertion; bold and underlined = deletion

[68]. At the neuronal level, the balance between GTP and GDP has been claimed to be part of the orchestration of the switch between proliferation, differentiation and neurite growth. In particular, the activated transcription of HTR1B results in enhanced neurite outgrowth of thalamic neurons, likely through the activity of G proteins, which switch from the activated to the de-activated state upon GTP → GDP exchange [99].

Where in the brain

As a protein, HTR1B is expressed mainly at the presynaptic level where it inhibits the neuronal firing as an autoreceptor. Moreover, it is expressed as a heteroreceptor on the surface of different neurons. HTR1D exerts the same activity as HTR1B, but it is likely mainly expressed at the post-synaptic level [76, 102]. In the human brain HTR1B is expressed at high levels in the substantia nigra and in the globus pallidus. Lower levels are present in the striatum, with the highest densities in the ventromedial parts, in the amygdala, in the hippocampus and in the septal region of the hypothalamus. Low density of HTR1B are found in the cortex with the exception of the medial occipital cortex. HTR1D is less abundant than HTR1B, and it is especially expressed in the ventral pallidus [175]. A similar pattern of distribution can be found in mice [90].

Diverse functions in different parts of the brain

Overall, the ablation of HTR1B leads to impulsive aggressiveness and increased sexual behavior, along with increased alcohol and cocaine intake in animal models [42, 129, 137, 145]. These phenotypes are dependent on intricate molecular activity across the central nervous system, with HTR1B providing activating or inhibiting effects according to the neuron’s surface on which it is expressed; HTR1B activation on the surface of a GABAergic neuron would result in a final excitatory activity, whilst the expression of HTR1B on the surface of a serotonergic neuron functionally associated with a glutamatergic network would result in inhibitory activity. Consistent with this, there has been reported evidence that HTR1B plays an excitatory role with regard to serotonergic neurons in the raphe nucleus [58], that it acts with an excitatory final effect on GABAergic networks in the suprachiasmatic nucleus [24], and that it acts with an inhibitory final effect on serotonergic release on the striatum [45] and in the frontal cortex and hippocampus [169]. Quite interestingly HTR1B seems to enhance the serotonin transmission in the caudal parts of the brain, whilst it inhibits the serotonin transmission in the rostral parts of it. Things may be fairly complicated though; it has been suggested that the activating or inhibitory events following HTR1B stimulation may actually depend on the frequency of stimulation

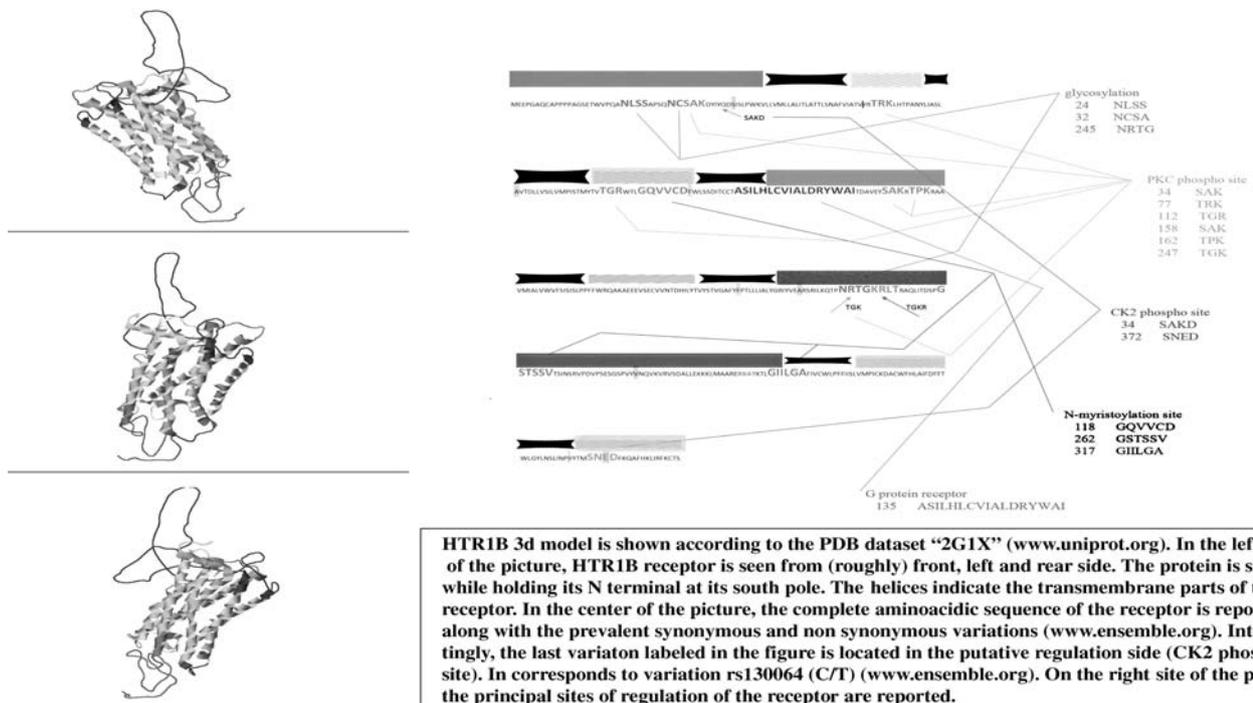


Fig. 1 HTR1B 3D molecular structure: the amino-acid sequence is shown. Relevant enzymatic sites are high lightened along with synonymous (*shadowed underlined*) and non synonymous (*shadowed not underlined*) variations

Table 3 Genetic association studies unraveling the association between substance dependence disorders and HTR1B variations

Reference	Investigated HTR1B snp	Sample	Ethnicity	Result	<i>P</i> level
[35]	A-161T; A1180G; 184/- 183; - 182/- 181; T-261G, C129T, G861C	166 subjects with cocaine abuse or dependence or alcohol abuse or dependence, 44 controls	Caucasian = 91 African/ American 93 Hispanic = 26 Other = 10	No significant association	Not significant
[88]	G861C, G-261T, C129T	347 subjects suffering from substance dependence and 146 healthy controls	370 Caucasian 123 African/ Americans	No significant association with substance dependence or with antisocial behavior	Not significant
[92]	G861C	242 female smoking initiators (127 with high and 115 with low nicotine dependence), 148 female smoking non-initiators	Caucasian	G861C GG genotype was associated with higher nicotine dependence	<i>P</i> =0.01; OR=2.29
[78]	G861C	394 psychiatric patients and 96 healthy subjects	Caucasians mainly	G861C C allele is associated with abuse disorder and MDD	<i>P</i> =0.007
[166]	G-511T; -504Bgl II; T-261G; A-161T; C129T; A772G; G861C; G1180A	158 alcohol-dependent cases with withdrawal symptoms and 149 control subjects	Asians	A-161T variant was found to be marginally associated with alcohol dependence: A allele was less represented in cases	<i>P</i> =0.01 (allele) <i>P</i> =0.041 (genotype)
[89]	G861C; D6S284	166 alcoholic criminal offenders, 261 relatives, 213 healthy controls. Southwestern American Indian tribe (<i>n</i> =418) with a high rate of alcoholism	Caucasian	In Finnish sib pairs, antisocial alcoholism showed significant evidence of linkage to HTR1B G861C. Alcoholic offenders have significantly higher HTR1B-861C allele frequency. In the Southwestern American Indian tribe, significant sib pair linkage of antisocial alcoholism to HTR1B G861C and to D6S284	<i>P</i> =0.04 <i>P</i> =0.005 <i>P</i> =0.01 <i>P</i> =0.01

Table 4 Genetic association studies unraveling the association between obsessive compulsive disorders and HTR1B variations

Reference	Investigated HTR1B snp	Sample	Ethnicity	Result	<i>P</i> level
[105]	G861C	32 families of OCD patients	Caucasian	The G allele of the G861C was overtransmitted to OCD patients	<i>P</i> <0.006
[106]	G861C; T371G	121 families of OCD patients	Caucasian	The G allele of the G861C was overtransmitted to OCD patients	<i>P</i> =0.02
[30]	G861C	72 trios of OCD patients	Caucasian	The G allele of the G861C was associated with worse obsessive symptoms, but not with diagnosis	<i>P</i> =0.034
[48]	G861C	48 trios of OCD patients	Caucasian	No significant association	Not significant
[93]	G861C	165 consecutive female probands with BN, 45 of which had either full or partial OCD syndrome	Caucasian	GG genotype was associated with full diagnosis of OCD in bulimic patients	<i>P</i> =0.01
[70]	G861C	71 OCD patients, 129 controls	Afrikaner population	No significant association	Not significant

OCD = obsessive compulsive disorder; BN = bulimia nervosa

Table 5 Genetic association studies unraveling the association between schizophrenia and HTR1B variations

Reference	Investigated HTR1B snp	Sample	Ethnicity	Result	<i>P</i> level
[74]	A-161T	110 schizophrenics and 215 controls	Asian	No significant association with schizophrenia	Not significant
[52]	T-261G, -182INS/DEL-181, A-161T, C129T and G861C	456 schizophrenics and 557 controls; 229 trios	Asian	No significant association with schizophrenia	Not significant
[78]	G861C	394 psychiatric patients and 96 healthy subjects	Caucasians mainly	No significant association with schizophrenia	Not significant

Table 6 Genetic association studies unraveling the association between suicidal behavior and HTR1B variations

Reference	Investigated HTR1B snp	Sample	Ethnicity	Result	<i>P</i> level
[176]	Four polymorphisms within three genes. The polymorphism related to the HTR1B was not polymorphic	226 suicide victims and 225 healthy control subjects	Caucasian	No significant association with suicidal behavior	Not significant
[141]	G861C	148 suicide attempters and 327 healthy controls	Caucasian	No significant association with suicidal behavior, or with suicide method or comorbidity	Not significant
[85]	G861C	Meta-analysis involving 789 cases and 1,247 control subjects	Various	No significant association with suicidal behavior	Not significant
[173]	G861C	106 suicide completers and 120 normal controls	Caucasian	No significant association with suicidal behavior	Not significant
[110]	G861C	163 suicide victims and 163 healthy controls	Japanese	No significant association with suicidal behavior	Not significant
[164]	G861C	363 suicide victims and 440 controls	Caucasian	No significant association with suicidal behavior	Not significant
[187]	Five 5-HT1B loci, including the A-161T	338 suicide victims and 358 controls	Caucasian	A-161T was associated with aggressive behavior	$P < 0.05$
[172]	A-161T	160 MDD patients and 160 normal controls	Asian	No significant association with suicidal behavior or with MDD or fluoxetine response	Not significant
[74]	A-161T	110 schizophrenic patients and 215 normal controls	Asian	No significant association with suicidal behavior or with aggressive behavior	Not significant
[78]	G861C	394 psychiatric patients and 96 healthy volunteers	Asian	No significant association with suicide, schizophrenia, alcoholism, bipolar disorder	Not significant
[122]	G861C	129 deliberately self-harming subjects, 329 controls	Caucasian	No significant association with self harming	Not significant
[77]	G861C; C129T	71 suicide victims; 107 non-suicides; 45 MDD, 79 non-MDD; 64 substance disorders, 60 without; 36 with pathological aggression, 42 without	Caucasian mainly	No association between gene and suicide; G allele was associated with lower 5-HT1B receptor binding	Not significant
[110]	G861C	163 suicide victims	Asian	No significant association	Not significant
[108]	G861C	145 patients with personality disorder	Caucasian = 90 Hispanic = 27 African/ American = 24 Other = 4	The G allele associated with a history of suicide attempts in white patients with personality disorders	$P = 0.01$

Table 7 Genetic association studies unraveling the association between personality disorders and HTR1B variations

Reference	Investigated HTR1B snp	Sample	Ethnicity	Result	<i>P</i> level
[171]	A-161T	209 young healthy subjects	Chinese	No significant association with schizophrenia	Not significant
[160]	G861C	164 alcoholic subjects	Caucasian	C allele was associated with antisocial personality	<i>P</i> =0.042 (Bonferroni correction)

[178], which may provide the neural networks with a refined tool to balance the noise–signal ratio.

From animals to humans: HTR1B in a translational approach

KO models

The body of knowledge about the postulated role of the HTR1B receptor in regulating brain functions, physiological processes, complex behaviors [130, 146], and possibly in participating in the genesis of several psychopathological conditions [34, 55, 62, 150] mainly comes from pre-clinical studies.

These pre-clinical studies include in vivo or in vitro pharmacological treatments with selective HTR1B receptor agonists and/or antagonists followed by the evaluation of specific neurochemical parameters and/or behavioral tests. Moreover, besides the use of pharmacological tools, the neurochemical setting and the response to specific behavioral tests have been evaluated in genetically modified animal mouse models such as constitutive knockout (KO) mice lacking HTR1B receptor generated by homologous recombination [145].

Since the early 1990s genetically modified rodents have been used to identify basal functions and behaviors impaired by the mutation of a gene of interest and thus the role of a specific protein. There are many advantages of using genetically-engineered mice to assess the influence of a given gene on a specific molecular target and/or specific behavior in a direct way. For example:

1. In mice the genetic background can be controlled and its genome is easily manipulable.
2. Cutting-edge technologies (including invasive ones) can be used.
3. A large number of biological functions of the mouse are similar to those of the human.

Mice lacking the HTR1B receptor subtype exhibit different changes in phenotypes, suggesting a major role for this serotonergic receptor subtype in mediating many functions (for a review of main phenotypic features see [162]). HTR1B KO mice do not exhibit any, or have few,

obvious developmental and behavioral defects in the absence of environmental or pharmacological challenges [37, 129, 145, 146]. However, by conducting behavioral tests, it has been demonstrated that these HTR1B KO mice show, among other less striking behavioral phenotypes, lower anxiety [66, 129], and increased aggressive behavior [145] and impulsivity [23] compared with its wild type (WT) control strain. These KO mice could be considered an animal model for the disease state of increased vulnerability to drug abuse, such as cocaine [136, 137], or to psychiatric disorders [56, 146, 186].

However, even if constitutive HTR1B KO mice are an extremely powerful tool in the study of the role of the HTR1B receptor in the brain, care must be taken in the interpretation of the data obtained using these mice. In fact, in the KO animals, the gene is negated during the embryonic stage and is thereafter absent for the entire life of the organism. The life-long ablation of the receptor causes compensatory changes to occur in the HTR1B KO mice that should be taken into consideration before drawing any conclusions regarding the analysis of the mutant phenotype. Compensatory changes that have been demonstrated in HTR1B KO mice affect different neurotransmitter systems in the brain such as the serotonergic [38, 62], the dopaminergic [6, 153], and the cholinergic [142] systems. These changes include altered neurotransmitter release [121, 169, 170] or turnover [6], rather than modify receptor expression or mediated functions [38, 61] in specific brain regions. In this regard, intracellular pathways transducing the receptor-mediated signal into the cells could also be affected by the life-long knockout of the gene. For example, Ase and colleagues found that the efficacy of G-protein coupling to HTR1A [5], mu-opioid and GABAB [6] receptors is decreased in HTR1B KO mice. Long-term receptor absence induces changes in gene expression as well. HTR1B KO mice have elevated striatal levels of Δ FosB and increased AP1 DNA-binding activity compared with their WT litter-mates [137].

On the whole, these compensatory responses to the constitutive deletion of HTR1B receptors are very likely to underlie some of the behavioral phenotypes observed in the HTR1B KO mice. Moreover, these regionally selective compensatory changes may contribute to explaining some of the observed discrepancies between the results obtained

with classical pharmacological tools, mainly HTR1B antagonists, and those obtained with HTR1B KO mice [186].

Another peculiarity of HTR1B protein is the characteristic of playing different roles depending on where they are located within the brain [129]; thus, the neuronal population in which these receptors are knocked out is another feature that may deeply influence the KO mice phenotype. Given this situation, in addition to the compensatory changes, the depletion of the HT1B receptor in the whole brain of the KO mice makes it difficult to define the relative contribution of these receptors in producing specific behavioral abnormalities. For example, it is impossible to discriminate the quite likely different if not opposite [11] role of the auto- or heteroreceptors in underlying a specific behavioral phenotype.

Conditional KO models

In addition to conventional KOs, alternative approaches can be used to manipulate the mouse genome in order to generate valid animal models. For example, conditional KOs allow investigation of a gene in a tissue-specific or time-controlled manner. Zhuang and collaborators, using the gene targeting technology, have developed a new strategy to re-express in KO the HTR1B missing protein in only specific brain areas or neuronal circuits where the receptor is normally expressed [186]. These rescue mice, together with inducible KO mice [164], may contribute in the future to identifying the neuronal circuits responsible for the different phenotypes observed in the HTR1B KO mice.

Finally, studies on HTR1B mRNA, which over-expresses itself in selected neuronal circuits using virally mediated gene transfer are worth mentioning [11, 36, 107]. This technique enables the study of the phenotypic impact of a gene product within selected anatomical regions avoiding, at the same time, possible developmental compensations characteristic of KO mice. Clark and coworkers have developed a virally mediated gene transfection strategy to express HTR1B in the dorsal raphe nucleus, demonstrating that the over-expression of this receptor in this area increases anxiety behavior specifically following stress exposure [36, 37]. A similar technique has also been used to increase the expression of the HTR1B in the nucleus accumbens (Nacc) [11, 107]. The over-expression of HTR1B in the Nacc sensitizes rats in the locomotor-stimulating and rewarding properties of cocaine [107] and seems to intensify the rewarding as well as the negative properties of cocaine [11].

On the whole these techniques allow us to evaluate the role of the HTR1B protein in mediating a specific phenotype, assessed by using specific tests, that is possibly related to human symptoms of disease. Nonetheless, it is evident that certain features of human behavior cannot be

reproduced in rodents (for example, suicide, concepts of self, self-reflection, consideration of others, or language [148]) and this may complicate the extrapolation of results obtained in animal tests to human symptoms. However, this is not the case in motivation, memory, and cognition for which there are many available behavioral tests that allowed us to evaluate the role of the HTR1B on different aspects of motivation [14, 23, 136–138] or memory and cognition [27, 28, 101, 118, 181, 182].

It is becoming clear that in the next few years the integration of results from animal models with new findings from humans (for example, ex vivo, neuroimaging, and genetic studies) will be needed to better understand how the HTR1B receptor affects various behaviors.

Motivation

Definition

Motivation is referred to as the set of reasons that determines one to engage in a particular behavior, and it is thought to be routed by the basic need to minimize physical pain and maximize pleasure. It is classically distinguished into appetitive vs consummatory behaviors [151]. Craig [43] figured out a four-phase shaped algorithm describing motivation:

1. Phase 1 is characterized by the “appetite” behavior, which is defined as the more variable and flexible, searching phase of a behavioral sequence.
2. Phase 2 is referred to as “consummatory,” which is the stereotypic phase that begins when the object of the first phase is recognized and achieved.
3. Phase 3, the “aversion” phase.
4. Phase IV, the “freedom from stimulus” phase.

Ethologists provided figures further describing these behaviors: the “psycho-hydraulic” [97], the hierarchical model [168], and the theories of Beach [13] and Pfaus [120] are some examples. A complete and recent review on this topic can be found in Ball and Balthazart [8].

Implications for psychiatric disorders

Motivation can be started upon environmental or internal stimuli, and, consistent with this, it is not constant over time. The fluctuant adaptation to stimuli can be viewed as the result of the balance between neural networks that initiate and maintain motivational/hedonic affective and emotional states and networks that progressively promote their banishment [159]. This mechanism, when maintained as a good balance, promotes behaviors shaped to adapt to the environmental cues. If an imbalance occurs, an hyper-reward mechanism

associated with the stimulus may facilitate compulsory seeking the stimulus [87]. This may be the hypothetical underlying mechanism associated with substance dependence. On the other hand, failed orchestration leading to the achievement of a constant and unresponsive retain of the neutral pole may facilitate a poor flexible hedonistic neutrality, resulting in a negative/depressive attitude; this may be reminding of some aspects of mood and schizophrenic disorders.

Functional neuroanatomy: focus on motivation

The brain structures that are associated with motivation have been classically identified as the mesolimbic system, the basal forebrain, and the associative areas of the cortex. The limbic system further provides the emotional and mnemonic computations to the output of these neuronal components. These structures compose an architecture whose detailed functional description is still incomplete. Nevertheless, there is evidence that [2]:

1. The mesolimbic system furnishes the dopaminergic drive to the motivational approach
2. The basal ganglia are involved in the association processes that are related to motivation
3. The hippocampus and the amygdala are essential in the storing and processing of memories and emotions

In particular, the basal ganglia, once thought to be primarily involved in the motor control, are also relevant for motivation; the relevance of the ventral pallidus for the reward and motivationally mediated functions has been convincingly demonstrated [157]. The striatum provides the principal inputs to the pallidus, while receiving and conveying information from the major afferent systems including the corticostriatal, the nigrostriatal, and the thalamostriatal structures. Moreover, afferents from the sensorimotor cortex terminate in the putamen (the internal part of the striatum) whilst association regions of the cortex terminate in the caudate nucleus (the external part of the striatum). The ventral striatum receives inputs from the hippocampus and amygdala (Fig. 2a). This way, motor, sensorimotor, affective, and mnemonic information are directed toward the striatum, processed in that structure and then directed toward the pallidus. The ventral part of the pallidus is the output source and directs the information toward the thalamus and to the cortex. This set of inputs and outputs likely concurs to compose the biological substrate that provides the flexibility required to adapt to stimuli and environmental cues, through the recruiting of memories and affective values, along with the applying of learning abilities and associative and cognitive skills. In addition, two other brain components are interlaced with the ventral pallidus: the nucleus accumbens (Nacc) and the dopaminergic input from

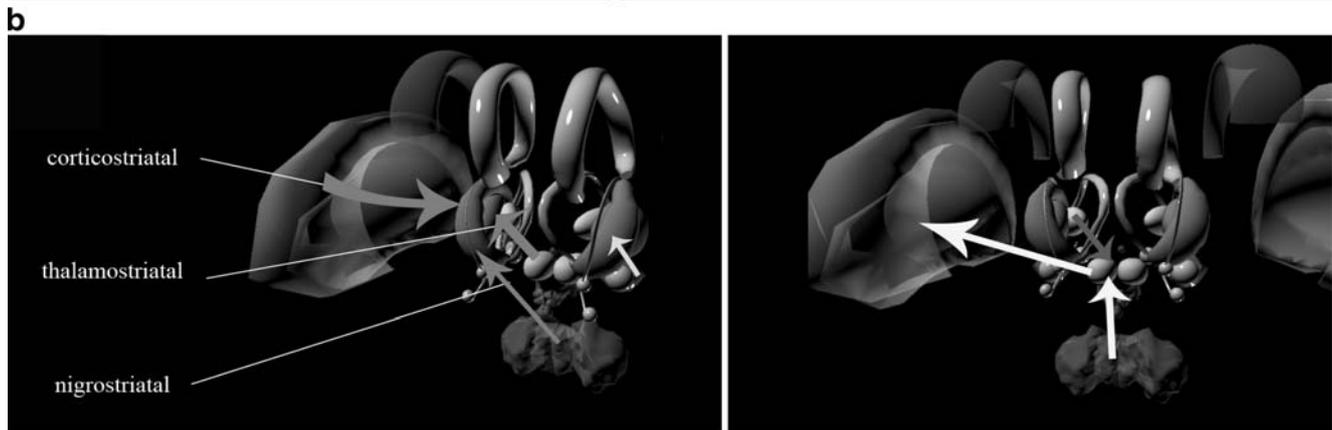
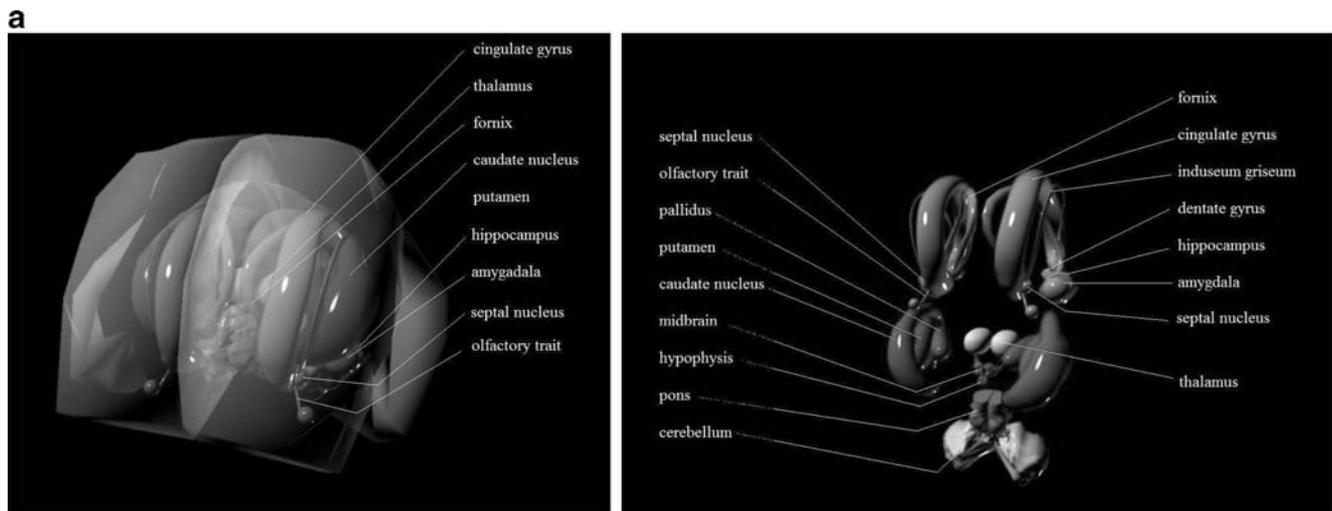
the ventral tegmental area. Both of them project to the ventral pallidus through dopaminergic connections, and the mesolimbic system projects to the Nacc as well, so that the ventral pallidus receives a double input arising from the mesolimbic system directly and from the Nacc. Moreover, the Nacc projects back to the ventral tegmental area, thus forming a short feedback system (Fig. 2b).

HTR1B and motivation

Manipulation of the Nacc through the direct injection of GABAergic agonists or AMPA antagonists or opioid or cannabis agonists results in modified eating and drug-seeking behaviors. This has been related to the disinhibition of the ventral pallidus caused by the inhibition of the Nacc [7, 29, 82, 133, 134, 166, 180]. This figure suggests a motivational impact refined by the Nacc (namely, the shell) on movement control. Notably, this disinhibition is not chaotic; it actually drives a set of behavioral patterns that are focused on eliciting pleasure, a goal that derives from the interplay between the mesolimbic system, the basal ganglia, the limbic system, and the cognitive and associative areas of the cortex [2]. Interestingly, HTR1B plays a pivotal role within these structures, being highly expressed in the basal ganglia [90]. Moreover, the serotonin system exerts inhibition of motivation directly from the raphe nucleus [10], thus suggesting that inhibiting the serotonergic system at the level of the Nacc or at the level of the raphe nucleus results in the same promotion of motivation, a redundant mechanism that likely enhances the flexibility of the system and enriches the cross-talking with other correlated systems.

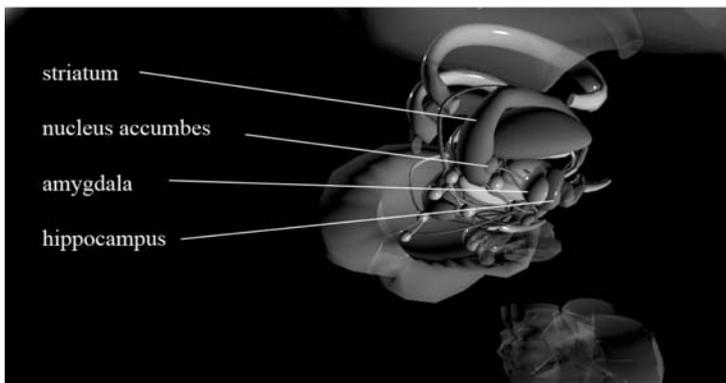
Within the basal ganglia, the main input of activation is mediated by glutamate from the striatum and dopamine from the mesolimbic system; within this system, HTR1B plays a role as a pre-synaptic receptor with inhibiting activity [144], probably with certain differences from the dorsal to the

Fig. 2 A 3D representation of the central nervous system (CNS). The CNS is seen from the upper left side. The cerebral structures are represented in an anatomically coherent way in the picture on the *left*. The model has been opened out in the picture on the *right*: the limbic system has moved upward, the thalamus, the midbrain, the hypophysis and the basal ganglia are in their original positions, and the pons and the cerebellum have moved downward. The cortex, the midbrain, the hypophysis, the hypothalamus and the corpus callosum are rendered transparent in the picture on the *left*. The cortex and the corpus callosum have been deleted in the picture on the *right*. The model has been opened out in **a** and **b** to detail the neurological pathways in which HTR1B is primarily involved. **a** The motor system. Striatum inputs are represented along with the functionality of the ventral striatum in movement controls. Moreover, the nucleus accumbens (Nacc)-mediated limbic input is detailed. **b** The mesolimbic dopaminergic input to the ventral pallidus is both direct and mediated by the Nacc. Moreover, the Nacc projects back to the ventral tegmental area

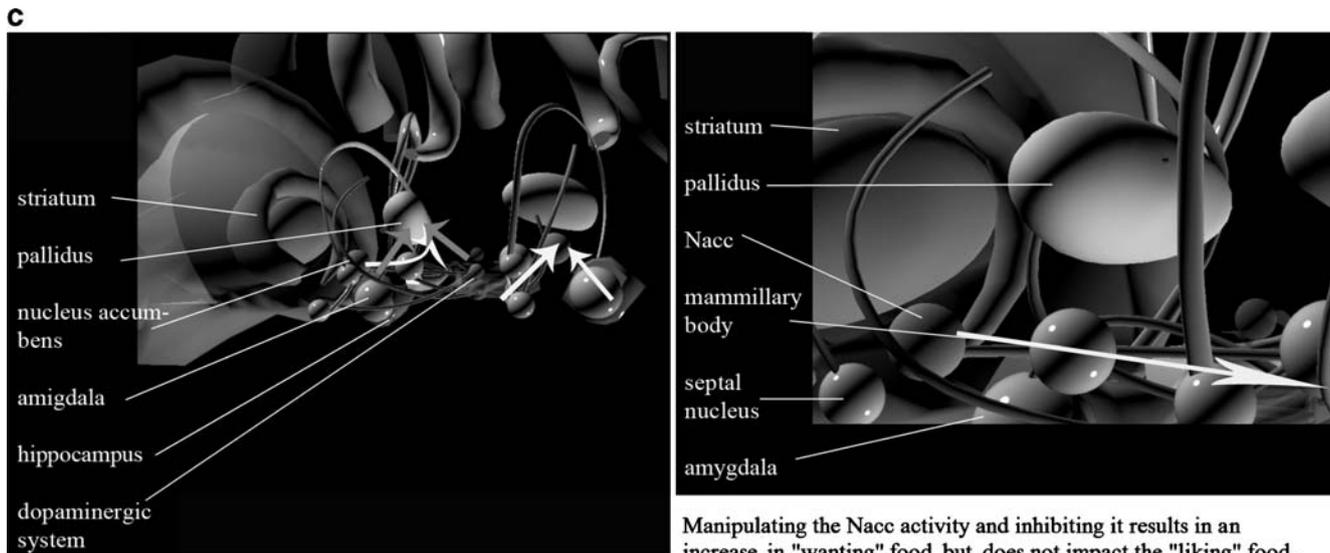


The striatum is the principal input brain structure receiving information from the cortex, from the thalamus and from the sub stantia nigra (three arrows on the left). Moreover, the ventral striatum receives inputs from the hippocampus and amygdala (small arrow on the right).

The ventral pallidum provides projections to the thalamus along with the substantia nigra. The thalamus then projects to the premotor and prefrontal cortices , giving rise to a circling formation which is enriched by the thalamic, limbic and basal ganglia computation.



It has been proposed that the nucleus accumbens provides the ventral pallidum with the limbic information forming the "limbic motor integration" to the accumenbs-pallidal system. The nucleus acumens is part of the mesolimbic dopaminergic system , whose activation is thought to be pivotal to the motivational behavior.



The mesolimbic system projects to the ventral pallidum (straight arrows) and to the Nacc (curved arrow) with dopaminergic efferences. At the same time, the Nacc projects to the ventral pallidum and mediates an inhibitory input to the structure (straight arrows). Moreover, the Nacc projects back to the ventral tegmental area (arrow not shown).

Manipulating the Nacc activity and inhibiting it results in an increase in "wanting" food but does not impact the "liking" food. Enhancing the expression of HTR1B in the shell of the Nacc results in an increased sensitivity to cocaine in animal models likely determined by a diminished inhibitory tone exerted by the serotonergic outputs from the Nacc to the ventral tegmental area (arrow).

Fig. 2 (continued)

ventral striatum. It has been reported that the direct injection of HTR1B agonist CP-93,129 into the dorsal striatum resulted in changed dopaminergic and serotonergic tones, only at a very high concentration [46]. The interplay between the deregulations of the monoaminergic systems after cocaine intake is characterized by a mediatory role exerted by serotonin with regard to the dopaminergic system [61], and a specific role of HTR1B is suggested; pretreatment with the RU24969—a HTR1B agonist—resulted in a leftward shift in cocaine self-administration [117], that is, in a reinforcement of the rewarding effect of cocaine, likely via serotonin-mediated enhancement of the dopamine concentration in the Nacc. Stimulation of the HTR1B leads to the downregulation of the serotonin tone in the striatum with a facilitator effect on the dopamine that results in higher, or more easily elicited, motivation for cocaine-seeking. Consistent with this figure, cocaine is able to increase the expression of HTR1B in the Nacc, likely eliciting the adaptation of the serotonergic–dopaminergic balance in the mesolimbic system [75, 113]. In a recent experiment, Barot and colleagues [11] specifically enhanced the expression of HTR1B in the medium spiny neurons of the shell of the Nacc that project toward the ventral tegmental area and obtained a different response in transferred animals and controls; transferred animals showed an enhanced response to low doses of cocaine with respect to the control animals whilst they showed avoidance behavior at higher cocaine doses. This suggests that serotonin mediates both the rewarding and the negative properties of cocaine use via

the HTR1B receptors. This may be consistent with the different role exerted by HTR1B, excitatory toward serotonin tone in the raphe, and inhibitory in other parts of the brain. So far, enhancing the expression of HTR1B in the Nacc would result in diminished serotonin activity with regard to the dopaminergic system in the ventral tegmental area, thus promoting a behavior more sensitive to cocaine in animals. At higher doses, the excitatory role of HTR1B in the raphe nuclei would prevail and the effect of dopaminergic neurons that innervate the raphe nuclei and exert a tonic excitation [49] would also prevail. This influence may be mutual; the activation of the HTR1B via microinjection of specific agonists in the VTA resulted in enhanced dopamine release in the Nacc, both during cocaine administration and without cocaine administration, and the GABAergic tone in the VTA was found to be inversely correlated with the activity of the HTR1B. That is, the serotonergic activity in the VTA results in an inhibition of the dopaminergic output with regard to the Nacc [112], and consistently plays a permissive role in the development of cocaine sensitization [45, 60, 124]. Interestingly, it has been reported that the mediatory effect of serotonin over dopaminergic tone is more specifically associated with HTR1B than with HTR1A [112, 115, 116]. So far, serotonin has played an inhibitory role with regard to the dopaminergic tone, and this inhibition can be counteracted by the activation of the HTR1B in the Nacc. Being speculative, one can hypothesize that more efficacious HTR1B transmission might play a protective role in substance dependence disorders, as confirmed by indepen-

dent studies [1, 33, 67, 98, 125, 126]. Consistent with this figure, Shippenberg and colleagues reported that the dopamine concentration in the Nacc was higher in HTR1B KO animals than in controls [153], and mice with both HTR1B knocked out showed a shorter latency period in meeting cocaine self-administration criteria [136]. Consistent with this, serotonin clearance was decreased in the event of HTR1B deletion [4]. Intriguingly, the antagonism as well as the absence of HTR1B resulted in higher 5HT concentration after paroxetine challenge in animal models [100]; acute stimulation leads to events that are opposite to those found in the event of chronic HTR1B inactivation. Some more consistent information is given by a recent experiment conducted by Faccidomo and colleagues [59]; the injection of a HTR1B agonist at the level of the raphe nuclei resulted in diminished aggressiveness, whilst enhanced aggressiveness was obtained after injection into the prefrontal cortex. Not only HTR1B has opposite behavioral effects in different parts of the brain, but it also shows different patterns of sensitiveness to enhanced serotonergic tone on a “neuro-geographic” basis; a challenge with paroxetine was found to be associated with more clear cut differences in HTR1B expression in the ventral hippocampus than in the prefrontal cortex of animals [100], thus suggesting that the functions of HTR1B in the ventral hippocampus are more sensitive to the activities of antidepressants. Finally, animal models suggest a specific role of HTR1B in socially relevant behaviors such as rearing and grooming; the microinjection of HTR1B agonist into the prefrontal cortex of mice resulted in increased rearing and grooming behavior along with an increased aggressiveness after social instigation. Intriguingly, HTR1A agonist threat was associated with a similar effect on social aggressiveness, but a reversed effect on rearing and grooming [32]. That is, HTR1B stimulation in the prefrontal cortex of animals may lead to an enhanced behavioral reactivity to the external stimuli, which results in an association with both disruptive and social promoting activities, this being decided likely according to the cognitive interpretation the animal carries out of the environmental conditions. In addition to all these lines of evidence, serotonergic and dopaminergic tones are not the only mediators implied in these mechanisms. For example, the cholinergic activity is pivotal to cognitive flexibility, and, interestingly, cholinergic neurons express HTR1B heteroreceptors [57, 135].

Memory

Definition

Memory is the ability to store information and to use it upon internal or external request. Memory is classically classified as declarative memory (conscious memories) and

non-declarative memory (unconscious memories). Declarative memories can be divided into episodic memories and semantic memories. Non-declarative memories are divided into several subgroups and these include classical conditioning, procedural memories, priming, and the working memory. The classical conditioning is referred to as the coupling of an unconditioned stimulus to a conditioned stimulus when they are repeatedly coupled over time; the procedural memories are those algorithms that operate at an automatically unconscious level, and priming is referred to as the event in which a particular object changes the response to the same object sequentially perceived. Working memory is the ability to keep in mind pieces of interlaced information according to the requirement of the moment. It is probable that different kinds of memories are stored in different neural networks, and in different formats as well [63]. Further, it is probable that memory consolidation and use is based upon molecular events located in the synaptic cleft. When a modification is achieved that resists interference, a trace memory is formed and can be used. These modifications can be short-lasting, based on the neuronal mediator release, and they are related to memory that lasts minutes or hours. Other memories last for a longer time, and they are supposedly based on long-lasting modification at the neurons, determined by changes in the expression profile of cells that lead to the molecular mechanisms of memory formation.

Molecular mechanisms of memory formation

The long-term potentiation (LTP) is considered to be the molecular basis of long-term memory; it is thought that external and internal events are represented in the brain as spatio-temporal patterns of neuronal activity that eventually determine the synaptic modifications that substantiate memory [18]. This model was formalized in the late 1940s by Hebb and Konorski [69, 86] and it is referred to as the coincidence detection rule, in which the synapse linking two cells is strengthened when cells are active at the same time. This effect was named LTP in 1973 [17] and it has a number of properties that strengthens its basic role in mnemonic information; it is established quickly and lasts for a long time, it is associative in that it depends on the co-occurrence of presynaptic activity and postsynaptic depolarization, it occurs only at potentiated synapses, and predominantly in the hippocampus [161]. Glutamate is considered to be the mediator of the LPT formation. Moreover, modification in the formation of the dendritic spines probably plays a major role in determining the plastic changes that allow LTP formation [161]. It has been proposed that the translational control is basic to the formation of LTP, a notion that envisages new strategies in the treatment of memory dysfunction-related disorders [41, 104].

Functional neuroanatomy: focus on memory

Memories are the sum of many forms of information including visual, tactual, spatial, olfactory, associative, auditory stimuli. Consequently, the locations in which this information is stored in the brain varies according to the kind of stimuli, this being dependent on the well-known functional differentiation of brain areas. For example, visual information is stored in the inferotemporal cortex, whilst concurrent different components of the event (spatial, tactile, olfactory, and so on), are stored in other areas. Therefore, any particular event is recalled to memory by the activation of a network of neuronal components, each of them engaging a specific processing site [161]. The hippocampus may play a role in integrating the timing and amount of flow of this information, processing it through the input from the deep basal ganglia, limbic system and cerebral cortex among which mutual interconnections exist. Nevertheless, other brain regions have been claimed to be central in the processing of the other forms of memory: the kind of memory that allows retention of small pieces of information temporarily available during the ongoing execution of mental operations, referred to as working memory, is thought to be retained in the posterior parietal cortex [132, 174]; the retaining and computation of this kind of information is essential to learning abilities and abstract thinking. Other forms of memory, such as the instrumental memory, are thought to be retained in other parts of the brain [72].

Functional neuroanatomy: episodic memory

The neuronal brain structure functionally related to the episodic memory is the medial temporal lobe, which includes the parahippocampal gyrus, the presubiculum, the subiculum, and the hippocampus. Other brain structures functionally related to this kind of memory are the anterior thalamic nucleus, the mammillary body, the fornix, and the prefrontal cortex. The flow of information coming from the activation of neural networks comes from the activation of senses and associative regions of the brain upon simple stimuli such as visual, auditory, tactile, and olfactory, but emotions and thoughts as well. Let us say that all these inputs are referred to the experience of having a dinner. This flow of information is conveyed in the parahippocampal region and subsequently to the hippocampus. Then, afterward, the information is processed in the dentate gyrus and transferred to the CA3 region, which corresponds to a specific zone in the hippocampal cortex. In that region, episodic memories are thought to be retrieved so that a similar dinner that might happen in the near future will be associated with the one we are remembering on the basis of the similar neuronal pattern of activation that is carried to

the CA3 region in the hippocampus. Moreover, once reactivated, the information stored in that part of the brain can elicit the emergence of all the correlated neuronal paths, so that a scent is able to recall to memory a whole scene. The hippocampus is not the final destination of a memory trace; when a process referred to as consolidation occurs, the information is thought to be moved from the hippocampal–cortex networks to the cortical–cortex ones. This event is crucial to the cognitive flexibility in order to face internal and external requests; memories are then not frozen in the hippocampus and they can be changed following the needs determined by the environment. While information is temporarily stored in the hippocampus (temporarily may mean years or minutes), the frontal lobes are believed to be primarily involved in the acquisition and temporal encoding of memory traces, as well as in their active retrieval in the absence of contextual stimulus [81, 119, 155], with a specific pattern of lateralization that depends on the kind of stimulus that is processed [25, 177]. Moreover, the involvement of the frontal and the posterior parietal cortex activities are thought to be associated with the ability to direct attention toward a certain focus, thus selecting the kind and amount of information that should be stored in the brain, on the basis of the superior associative activity of the brain [132, 174]. Consistent with this, deregulation of these mechanisms is associated with impaired memory, or with the production of false memories, or with a biased processing of memories so that, for example, negative events are preferentially stored and recalled, which may be one of the disrupted neural networks that underpins depressive disorders.

Functional neuroanatomy: semantic memory

Facts and concepts not related to any specific memory are the objects of the semantic memory. Examples are the ability to name a thing, to recall the common color of an object, to understand single words. There is evidence that the semantic memory is localized in the frontal cortex and in the anterior and inferolateral temporal lobes [9, 95, 123]. It is considered to be independent from the episodic memory, and, consistently, semantic and episodic memories decline independently of one another in Alzheimer's disease [65].

Functional neuroanatomy: classical conditioning and working memory

The classical conditioning is referred to as the event of the coupling between a unconditioned and a conditioned stimulus after they have been paired together repeatedly. It can be associated with autonomic responses, in the case of fear, for example, or with motor responses. The amygdala and the basolateral limbic system, which includes the

dorsomedial thalamic nuclei, the area subcallosa, and the stria terminalis, are relevant for autonomic conditioning, whilst the cerebellum is relevant for motor conditioning. Working memory is classically associated with the functions of the prefrontal cortex, but virtually every part of the cortex is engaged in the processing of information, depending on which task is being performed. Interestingly, spatially related information is preferably processed by the regions of the right side, whilst phonological tasks are computed in the left side of the brain. Nonetheless, the most difficult tasks activate all the brain regions in a fashion that is independent of the kind of stimulus [109].

Implications for psychiatric disorders

Memory- or mnemonic-related functions are impaired during psychiatric suffering. In particular, depressive disorder was found to be associated with impaired function of the hippocampus, the parahippocampal gyrus, the prefrontal cortex, the cingulate cortex, and the parietal regions [147, 179]; this deregulation was found to be associated with a higher rate of false memories, which, quite interestingly, often show a prominent negative affective meaning [64, 184]. This may be one of the biological events that enhances the risk of experiencing a depressive episode. Interestingly, antidepressant treatment proved to be effective in restoring normal memory activity [73]. Memory function was found to be impaired in bipolar patients and their relatives [20, 83, 128] and in schizophrenic patients as well [71, 91, 131]. Moreover, working memory and executive functions have been claimed to be promising endophenotypes through which early signs of psychotic disease can be detected [12, 16]. Finally, the conditioning events related to the activation of the amygdala have been associated with psychiatric disorders in a consistent number of reports (reviewed in Quirk and Gehlert [127]).

HTR1B and memory

The relevance of HTR1B in memory tasks is reported by several lines of evidence; activation of HTR1B results in an impaired spatial learning task [26], and, interestingly, the stimulation of HTR1B is associated with neophobic reactions when exploring unknown objects [26]. This latter piece of evidence was not replicated in HTR1B KO animals [101], even though HTR1B KO mice showed enhanced locomotor behavior in an enriched environment compared with WT animals. This was commented on as a possible effect of the major impulsivity that is classically associated with the deletion of the serotonin receptor 1B, and a parallelism with the syndrome of “overattention” that is found in schizophrenia was suggested [101]. Interestingly, in the afore-mentioned study HTR1B KO mice did not

show habituation to the environment, which was interpreted as an impairment of memory functions. In 2003, Buhot and colleagues confirmed that HTR1B KO animals presented with higher flexibility in the acquisition of spatial preference memory task, and a decreased ability in a working memory task with intermediate and long delays. This is suggestive of an impairment in the ability to keep memories of functionally associated events in order to use them for a specific purpose, and to facilitate the flexibility of cognitive ability, at least for simple tasks [27]. These events are in line with the notion that different kinds of memories are stored in specific neural networks and with the aforementioned different role played by HTR1B in different parts of the brain. In particular, the working memory tasks involve an efficient communication between the limbic structures and the prefrontal cortex, whilst the spatial memory is likely more related to the interplay between areas associated with visual stimuli, the hippocampus and postero-parietal cortices. In these networks, the role of HTR1B is likely associated with the impact of the serotonergically mediated glutamatergic input that arises from the raphe nuclei to the cortex and of the cholinergic input from the cholinergic structures in the basal forebrain to the cortex [27]. Thus, the absence of HTR1B results in a lack of inhibition in the networks that regulate the information flow that is necessary for the cognitive computation related to spatial navigation. Interestingly, it was reported that the difference between WT and HTR1B KO mice is more evident when animals are challenged with difficult tasks that require higher cognitive flexibility [181, 182]. This can be related to the fact that HTR1B activity results in a down-regulation of the cholinergic tone in the hippocampus and in enhanced cholinergic tone in the frontal cortex [31, 40]. Moreover, HTR1B are expressed on terminals of retinal ganglion cells in the superior colliculus [22] where they control visual attentional processes with an inhibitory role [21]; uninhibited visual activity may be intuitively related to enhanced ability in spatial tests. Another relevant hint is provided by the evidence that HTR1B KO animals show an increased pattern of prepulse inhibition compared with WT animals. This may be dependent on the higher cholinergic tone in the cortex associated with HTR1B deactivation, which would provide the animal with a keener—and less flexible—attention ability with regard to stimuli [54]. This may have a very relevant impact on the pathophysiology related to the obsessive compulsive disorder [150], even though recent experiments on animals suggest that the hyper-reactivity of mice deprived of the HTR1B may be more related to a deregulated startle reactivity [50], a behavior closer to impulsivity in our opinion. Consistent with this, it has been suggested that impulsivity and not memory is mainly impaired in HTR1B KO animals [118].

Genetic association studies

The mechanisms described above suggest that the variation in the activity of the HTR1B should be associated with an impact on human behavior, including psychiatric phenotypes; impaired orchestration of motivation and memory may likely be associated with a set of well-known clusters of symptoms shown by psychiatric patients, by including diagnoses as diverse as substance abuse disorders, mood disorders, anxiety disorders, and the psychotic spectrum. Nonetheless, the genetic association studies conducted so far provided poor evidence for this statement; moreover, no specific genetic association study involving the HTR1B has been conducted on memory and motivation so far. The most relevant results are reported in Tables 3, 4, 5, 6, 7.

Substance-related disorders

Overall, the most consistent findings are reported for substance abuse disorders. In 1998, Lappalainen and colleagues [89] analyzed two variations located in the HTR1B, namely the G861C and a closely linked short-tandem repeat locus, D6S284. Authors collected a large sample of 640 Finnish subjects, including 166 alcoholic criminal offenders, 261 relatives, and 213 healthy controls. Further, they analyzed the same set of variations in a large multigenerational family derived from a Southwestern American Indian tribe ($n=418$) with a high rate of alcoholism. The design of the study is of particular interest because it combines the analysis of cases and controls with the analysis of the pattern of heredity of those mutations and their correlation with the risk of alcoholism. Moreover, the sample size is one of the largest ever investigated in this field. Nonetheless, the strength of the association was weak for alcoholism alone ($0.05 < P < 0.06$). Interestingly, a stronger association was found when antisocial personality disorder was considered in association with alcoholism ($P=0.005$). The investigation in the American Indian tribe confirmed these trends ($P=0.01$). Despite the drawbacks that characterize the investigation (for example, incomplete gene coverage), this finding first suggests that a variation in the genetic framework of HTR1B leads to a pervasive pathological attitude that results in a personality disorder in association with a tendency to consume alcohol, rather than in alcoholism alone. This difference is quite interesting as it could underline a specific regulation that separates Axis I from Axis II disorders. Unfortunately, knowledge in this field is still too incomplete to allow any figure to be drawn other than a highly speculative one. The findings reported by Lappalainen and colleagues were further enriched by the observation that the variation found to be associated with alcoholism in antisocial personality disorder was actually associated with a different expression of HTR1B in the

prefrontal cortex of subjects, that is, the G allele at 861 associated with 20% less HTR1B expression compared with the C allele [77]. This is highly consistent with the evidence reported from animal models that demonstrated that the stimulation of HTR1B in the prefrontal cortices of mice resulted in different patterns of aggressiveness. The same study [77] failed to demonstrate a difference between suicidal behavior or alcoholism-related disorders; this may be related to the small sample sizes that were obtained after classification in the different diagnostic clusters.

Obsessive compulsive disorder

The G861C variation has been quite extensively analyzed in OCD patients as well, and reported quite consistent results as detailed in Table 7. In particular, the G allele, which was found to be associated with a lower expression profile in the PFC of subjects, was found to be at risk of obsessive symptoms, or to be associated with a worse presentation of symptoms. The conflicting results [48, 70] may be associated with underpowered samples [48] or with the analysis in non-Caucasian samples [70]; diverse ethnicities may show profound differences in the genetic predisposition to psychiatric disorders, the case of the well-known long/short variation in the promoter of the serotonin transporter gene being an emblematic example in that there is some evidence that it behaves within opposite paths in Caucasian vs Asian samples [158].

Psychosis and bipolar disorders

Despite the fact that HTR1B mRNA was found to be differently represented (upregulated) in the brains of schizophrenic and bipolar patients compared with controls [96], the genetic association studies that have been performed in these populations did not cast conclusive results. The most relevant studies performed on schizophrenic samples are reported in Table 5. The absence of results is quite surprising in that it has been demonstrated that variations in the activity of the HTR1B result in altered measures of central processing information in animals, that is, significant variations in startle reactivity, habituation, and prepulse inhibition [53, 54]. In particular, HTR1B is thought to decrease prepulse inhibition and habituation, whilst HTR1A showed opposite effects in mice [56]. These dimensions have been shown to be deficient in schizophrenic patients, but a correlation with the investigated variations located in the HTR1B and the schizophrenic phenotype did not sustain this relevance.

Suicidal behavior

Aggressiveness and impulsiveness are characteristic phenotypes derived from the absence of HTR1B in animal

models. This evidence attracted the attention of researchers interested in the genetic background that predisposes to suicidal acts as far as a high degree of impulsiveness and aggressiveness are associated with that behavior. Unfortunately, although extensively investigated, the association between HTR1B and suicidal behavior was not demonstrated as reported in Table 3. The reasons for this inconsistent evidence may be associated with the underpowered samples that characterize most of the investigation. Moreover, the absence of a complete coverage of genetic variations is more often the rule rather than the exception in the literature, and the lack of investigation of the molecular path associated with the activation of HTR1B further impairs the possibility of accounting for the impact of HTR1B on psychiatric suffering. These issues, along with other methodological suggestions, have been discussed in more detail in other papers we have published on the topic [51, 149].

Conclusion

The molecular and neuroanatomical mechanisms that sustain the relevance of HTR1B with regard to psychiatric suffering have been reviewed in this paper in the light of two brain functions as relevant as motivation and memory. The experiments conducted on animal models seem to extensively sustain the pivotal role of HTR1B in the functioning of high level brain functions, but genetic association analyses in human samples could confirm this association only for obsessive compulsive disorder and substance-related disorders, especially in the presence of personality disorders. In particular, an impaired balance in HTR1B associated with the presence of the G allele at the G861C variation proved to be functionally relevant and associated with obsessive compulsive disorders as well as with alcohol dependence. The lower HTR1B expression in the PFC, which was found to be associated with the G allele at G861C may be the cause of a dopaminergic imbalance in the PFC cortex that would result in complex imbalances responsible for those psychiatric deregulations. Intriguingly, this seem to be fairly specific: schizophrenic and bipolar disorders were consistently found not to be associated with this variation, and nor was suicide behavior. It could be said that greater anxiety develops from the disrupted function of HTR1B, which is driven toward a varied set of compulsions being activated in the context of personality disorder, substance use disorder or obsessive compulsive disorder. Although suggestive, this figure seems to be only partially supported by genetic association analyses in that not all the studies confirmed the significant association results. This may depend on the poor complexity of the approach that

characterizes most investigations, some of the more relevant aspects of this incompleteness are:

1. Psychiatric phenotypes are uneasily reduced to a biological dichotomic variable such as single genetic variations. The search for associations between genetic variants and psychological dimensions may provide better results. It has been recently reported that a haplotype in the HTR1B gene (rs11568817, rs130058, rs6296, rs6297, rs13212041) impacts on the feeling of anger in male healthy volunteers, with the low expression haplotype being associated with greater anger and hostility [39].
2. It may be hypothesized that a set of biological events might adapt to the functional variations that are genetically driven and recombine the homeostasis or, at least, a kind of allostatic equilibrium. This allostasis produces a biological load that may actually be associated with the risk of experiencing psychiatric suffering, but that would result in a fully diagnosed psychiatric episode only at its very extreme poles. In other words, the co-occurrence of other events, which may be both biological and psychological in nature, are likely needed to turn the genetic liability associated with HTR1B variation into a full episode of disease as depicted in DSM IV. Thus, the investigations meant to unravel the associations between the genetic background and behavioral experience should take into strict and detailed account the psychological and biological events that characterize, and stratify, the samples, both cases and controls. The need to include in the analysis the psychological events in cases and controls should characterize the next investigations in this field, along with a more complex molecular approach to the matter. For example, other mutations should be taken into account, ranging from the complete coverage of the HTR1B gene, through a tag approach, to analysis of the variations that are detailed in this paper.
3. Copy number variations, epigenetic controls, epistasis between genes involved in the same molecular mechanisms as HTR1B, the analysis of the impact of micro RNAs on the expression of HTR1B and the investigation of possible mRNA editing controls should be scheduled in the next investigations. For example, there is evidence that the p11 controls the activity of HTR1B [167, 185], so that every functional genetic variation located in the HTR1B could be regulated and counteracted in its functional imbalance by the activity of such a protein.
4. There is an interaction between HTR1B and HTR2B [80], and between HTR1B and aging as well [28, 154]. Moreover, the role with regard to nociception of HTR1B has been extensively investigated [15, 84, 94, 111, 139], and a modulation of psychiatric disruption in

terms of an altered nociceptive signal computation could be hypothesized.

The main result of this review is that the gap between the physiology that sustains the relevance of HTR1B in psychiatric-related events and reactions and the poor and sparse evidence of human samples, may be bridged by a far more complex and deep knowledge of the molecular mechanisms associated with this receptor and of its gene, in specific parts of the brain.

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