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Genetic, epigenetic and posttranscriptional mechanisms for treatment of major depression: the 5-HT$_{1A}$ receptor gene as a paradigm

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Major depression and anxiety are highly prevalent and involve chronic dysregulation of serotonin, but they remain poorly understood. Here, we review novel transcriptional (genetic, epigenetic) and posttranscriptional (microRNA, alternative splicing) mechanisms implicated in mental illness, focusing on a key serotonin-related regulator, the serotonin 1A (5-HT$_{1A}$) receptor. Functional single-nucleotide polymorphisms and stress-induced DNA methylation of the 5-HT$_{1A}$ promoter converge to differentially alter pre- and postsynaptic 5-HT$_{1A}$ receptor expression associated with major depression and reduced therapeutic response to serotonergic antidepressants. Major depression is also associated with altered levels of splice factors and microRNA, posttranscriptional mechanisms that regulate RNA stability. The human 5-HT$_{1A}$ 3′-untranslated region is alternatively spliced, removing microRNA sites and increasing 5-HT$_{1A}$ expression, which is reduced in major depression and may be genotype-dependent. Thus, the 5-HT$_{1A}$ receptor gene illustrates the convergence of genetic, epigenetic and posttranscriptional mechanisms in gene expression, neurodevelopment and neuroplasticity, and major depression. Understanding gene regulatory mechanisms could enhance the detection, categorization and personalized treatment of major depression.

Introduction

Major depression is a serious illness, with 15% lifetime prevalence; it is ranked number 1 in terms of global burden of disease.[1] Both genetic and environmental factors are thought to contribute to major depression. Anxiety and depression are closely related genetically,[2] and are often comorbid. They are thought to involve reduced serotonin (5-HT) activity,[3–6] which is reversed by selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine.[7–11] However, treatment with SSRIs for 5 to 8 weeks is required for remission, which occurs in only 30% of patients.[12–14] Thus, although the serotonin system is involved in major depression and antidepressant actions, a better understanding of how the system is regulated over time is needed to further enhance the effectiveness of treatment.[8,9]

The brain 5-HT system originates in the raphe nuclei, which projects widely[15] to innervate corticolimbic systems involved in stress,[16] anxiety,[17] depression[18] and cognitive function.[19] The levels of 5-HT are determined primarily by expression of the rate-limiting enzyme tryptophan hydroxylase-2 (TPH2);[20] by reuptake via the 5-HT transporter (5-HTT), which is the target of SSRI antidepressants;[21] and by the levels of 5-HT$_{1A}$ autoreceptors that negatively regulate 5-HT neuronal firing.[22] Increased levels of 5-HT$_{1A}$ autoreceptors, which would reduce 5-HT activity, are seen in depressed patients and in the raphe tissue of people with depression who died by suicide (Fig. 1).[23,24] By blocking the 5-HTT, SSRIs allow released 5-HT to remain in the synaptic space and persistently activate receptors on target neurons.[25] However, 5-HT is also augmented in the raphe, which activates the 5-HT$_{1A}$ autoreceptor and mediates feedback inhibition to reduce 5-HT neuron firing, negating the effect of SSRI treatment.[25] But after days to weeks of SSRI treatment, the 5-HT$_{1A}$ autoreceptor desensitizes.[26,27] Although acute desensitization mechanisms such as uncoupling and internalization are occurring,[28–30] the long time course suggests a role for transcriptional regulation.[31] Altered regulation of the genes for 5-HTT and 5-HT$_{1A}$ receptors could alter 5-HT activity, predispose to depression and affect SSRI response.

In this review, we discuss how different transcriptional and posttranscriptional mechanisms alter the regulation of these key genes in depression, focusing on the 5-HT$_{1A}$ receptor gene (Fig. 2). The 5-HT$_{1A}$ receptor gene provides an example of how global alterations in these regulatory mechanisms

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may affect the expression of many genes. We present evidence from human and animal model studies that link multiple regulatory changes with increased risk of depression, anxiety and resistance to SSRI treatment.

Genetic risk: transcriptional mechanisms

A consistent finding in genome-wide association studies has been that single-nucleotide polymorphisms (SNPs) associated with depression are localized in noncoding and often gene-regulatory or untranslated regions.[2] Another consistent finding has been the overlap of genes associated with different mental illnesses, the greatest similarity being between depression and anxiety.[2] This implicates altered transcriptional regulation as a potential primary change that confers genetic risk for depression and related mental illnesses.

Functional 5-HT polymorphisms and major depression

In the 5-HT system, the 5-HTTLPR (long polymorphic repeat) located in the promoter region of the 5-HTT gene was the first to be associated with anxiety-like behaviour and depression.[32,33] The 5-HTTLPR ss genotype reduces 5-HTT transcription in vitro[34] and has been associated with reduced 5-HTT expression in blood cells,[32] although this association has not been detected in the brain.[35] The 5-HTT ss genotype has been associated with major depression and resistance to SSRI treatment in many studies,[36] but not all.[37] Subsequently, the 5-HT_{1A} rs6295 SNP was identified,[38] and the GG genotype was shown to lead to overexpression of 5-HT_{1A} autoreceptors by preventing binding of the repressors *DEAF1/NUDR* and *HES5/HES1* (Fig. 2). Because *DEAF1* functions as an *HTR1A* repressor in raphe cells, but as an enhancer in postsynaptic neuronal cells,[39] the rs6295 G allele should increase 5-HT_{1A} autoreceptor expression, but reduce postsynaptic 5-HT_{1A} heteroreceptor levels. In support of this, recent studies have shown an association of the rs6295 GG genotype with reduced 5-HT_{1A} receptors in cortical and hippocampal tissues,[40,41] while there is increased 5-HT_{1A} binding in the raphe.[23,41] Similarly, knockout of *Deaf1* in mice induces raphe 5-HT_{1A} autoreceptors while reducing prefrontal cortical 5-HT_{1A} expression,[42] implicating *DEAF1* in the effects of the rs6295 polymorphism, although other factors may also participate.[40] Thus, rs6295 is a functional promoter polymorphism that modifies 5-HT_{1A} receptor gene expression in a region-specific manner.

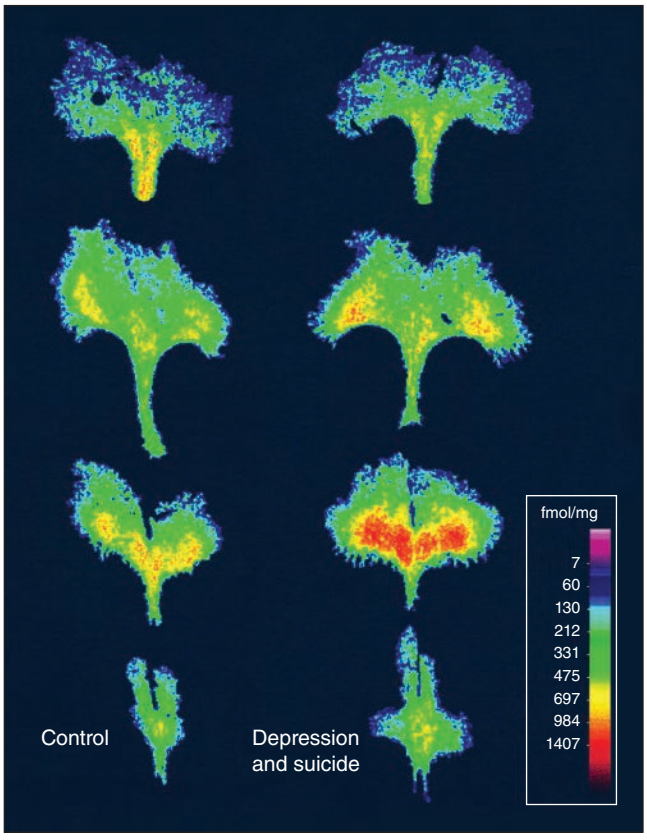

Fig. 1: Increased levels of 5-HT_{1A} autoreceptors in the dorsal raphe of depressed individuals who died by suicide compared with the brains of healthy people. Digitized images of [^{3}H]DPAT binding to 5-HT_{1A} receptors at 4 rostral-to-caudal levels of the dorsal raphe from a representative control participant (left) and an age-matched person who had major depression and died by suicide (right). Reproduced from Stockmeier and colleagues[24] with permission from *Journal of Neuroscience*.

In previous reviews, we presented evidence that, similar to the 5-HTTLPR, the *HTR1A* rs6295 risk genotype (G allele or GG genotype) has been associated with major depression and resistance to the antidepressant actions of SSRIs and atypical antipsychotics in multiple studies.[43,44] Associations of rs6295 with major and bipolar depression are supported by meta-analyses,[45–47] although no association with anxiety or depression symptoms was reported in a large cohort of healthy people.[48] Furthermore, several other 5-HT-, monoamine-, or stress-related genes have also been associated with major depression.[49,50]

The *HTR1A* G carrier or GG genotype has also been associated with increased 5-HT_{1A} autoreceptors,[23,41] major depression,[51] amygdala reactivity to fearful stimuli[52–56] and increased hippocampal volume.[57] In addition, associations have been reported between the G carrier or the GG genotype and disordered eating in female adolescents,[58] panic disorder[59] or panic disorder without agoraphobia,[60] substance abuse and psychiatric hospitalization.[61] Depressed patients with the C allele showed enhanced response to transcranial magnetic stimulation,[62] similar to the association with SSRI response. The rs6295 polymorphism was associated with SSRI-induced adverse effects: diarrhea (G allele) and sexual apathy (C allele).[63] One study found that the rs6295 G allele was associated with greater (rather than reduced) response to SSRI treatment.[64] Therefore, it was important to test in animal models whether altered transcription of 5-HT_{1A} autoreceptors or heteroreceptors has any influence on behaviour or response to antidepressants.

Genetic interactions

Several genetic interactions of rs6295 with risk alleles, such as 5-HTTLPR,[65] *HTR2A* rs6311, or *BDNF* rs6265 SNPs in major depression, have been reported.[66] The *HTR1A* rs6295

polymorphism showed strong interaction with life stress and *BDNF* rs6265 (Val66Met) for major depression[67] and for treatment-resistant depression.[68] The *BDNF* Val66Met has the highest level of functionality (class 3[69]), having been shown to phenocopy reduced *BDNF* trafficking and secretion in a mouse knockin model.[70] In the human brain, the *BDNF* Met allele was associated with reduced 5-HT$_{1A}$ binding in 1 study,[71] but not others.[72,73] In a recent study, 3 or more combined *HTR1A* and *BDNF* risk alleles associated increase 5-HT$_{1A}$ receptor binding in cortical subregions.[74] In contrast, the *COMT* Val158Met rs4680 genotype oppositely altered the rs6295 association with interferon-induced depression.[75] Perhaps most intriguing is an interaction of the *HTR1A* rs6295 genotype with the phospholysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP*) gene in major depression, seen in Utah and Ashkenazi populations. Subsequently, *LHPP* was identified in a genome-wide association study of female melancholic depression[76] and a Mexican–American major depression cohort.[77] Recently, *LHPP* has been shown to function as a tumour suppressor,[78] and it may affect 5-HT$_{1A}$ receptor signalling, but this remains to be addressed.[79]

HTR1A *rs6295 and phenotypic/brain network alterations*

In terms of physiologic differences, rs6295 G carriers showed thermal hypoalgesia[80] and increased depression after lumbar surgery.[81] In panic patients with disorder/agoraphobia with the GG genotype, there was increased amygdala reactivity to threat or safety cues, behavioural avoidance and reduced response to cognitive behavioural therapy,[82] and increased contextual fear in healthy participants.[83] Similarly, in panic disorder the G allele was associated with increased amygdala reactivity to fearful faces,[56] while in healthy controls an opposite association was seen,[52] suggesting that the influence of the polymorphism may depend on the disease state.[22] In small studies of the elderly, the C allele was protective against depressed mood in healthy athletes compared to non-athletes (n = 55 v. 58)[84] and enhanced remission to 4-week citalopram treatment in people recently diagnosed with depression (n = 19).[85] In addition, the G allele was inversely correlated with parasympathetic tone, which was associated with reduced anxiety in healthy participants (n = 1141).[86] Thus, the rs6295 G allele associates with depression and anxiety phenotypes, while the C allele may be protective.

The *HTR1A* rs6295 genotype also associates with alterations in brain activity that may underlie depression. Brain imaging studies of people with bipolar disorder in the depressed state have shown that the GG genotype is associated with increased amygdala–ventrolateral prefrontal cortex (PFC) connectivity, and changes in corticolimbic connectivity correlated with depression severity.[87] In a study of 99 healthy Japanese people, the G carriers were associated with decreased functional connectivity of the default mode network (DMN) in the dorsolateral and ventromedial PFC, and with

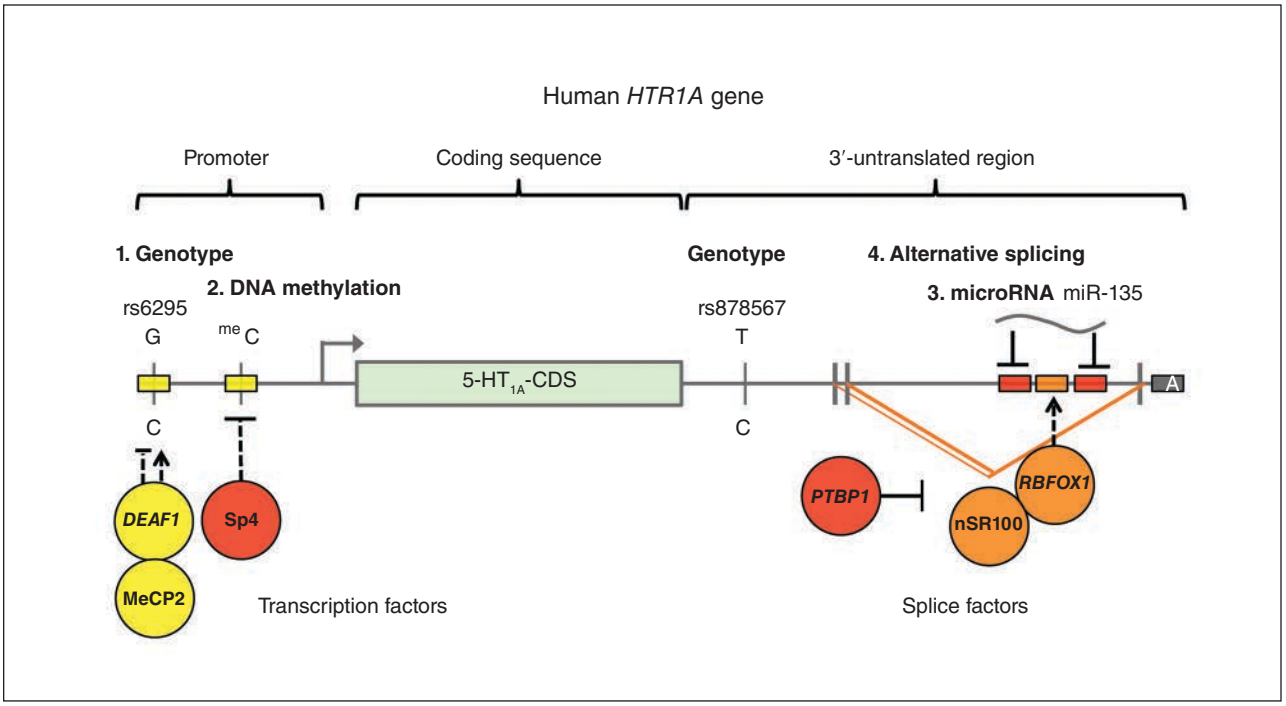

Fig. 2: Model of key transcriptional, epigenetic and posttranscriptional regulatory sites of the human *HTR1A* gene. The promoter, coding sequence and 3′-untranslated region of the 5-HT$_{1A}$ receptor gene are shown, highlighting key regulatory regions altered in major depression by genotype (SNPs rs6295 and rs878567), DNA methylation (Sp4 site), microRNA (miR-135), and alternative splicing. Shown are the transcription start (arrow) and polyadenylation (A) sites, DNA-binding transcription factors (*DEAF1*, MeCP2, Sp4) and RNA-binding splice factors (*PTBP1*, nSR100, *RBFOX1*) implicated. Activation (arrow) or inhibition (block) may be dependent (dashed line) on genotype, methylation or splicing. 5-HT = serotonin; CDS = coding sequence; SNP = single nucleotide polymorphism.

reduced salience network connectivity in the ventromedial PFC and the subgenual anterior cingulate cortex.[88] Abnormalities in these networks, particularly the DMN, have been associated with major depression, and with the 5-HTTLPR ss genotype,[89,90] as well as with other 5-HT-, monoamine- or neuropeptide-related genes.[91] Other studies have shown that levels of raphe and cortical 5-HT_{1A} receptors detected using [^{11}C]WAY100635 binding are increased in depressed patients and correlate with cortical thickness and tract number in the posterior cingulate cortex, part of the DMN.[92] Conversely, in healthy people [^{11}C]WAY100635 binding was negatively correlated with posterior cingulate cortex and medial dorsal PFC activity.[93] These studies suggest that the 5-HT_{1A} receptor regulates the DMN, but in opposite ways in healthy people compared to depressed people. Increased activity of the DMN could correlate with the increased rumination and self-focus observed in major depression.[94]

Cognitive function was also affected in people with the G allele, with poorer performance on the Iowa gambling test (in combination with 5-HTTLPR ss)[95] and impaired working memory in premenstrual dysphoric disorder.[96] Conversely, depressed patients with the CC genotype showed better performance in a battery of 9 cognitive tests.[97] In healthy Han Chinese people, the CG/GG genotype has been linked with difficulty to identify one's own feelings and in forming close attachments[98] or romantic relationships,[99] which could relate to depression susceptibility. In panic disorder, the CC genotype is associated with increased fractional anisotropy of the left cingulate gyrus.[100] In addition, 5-HT_{1A} receptors ([^{18}F]-FCWAY binding sites) are reduced in the anterior cingulate cortex in panic disorder,[101] and the GG genotype is associated with augmented avoidance and reduced enhancement of anterior cingulate cortex activity by therapy.[82] These imaging findings suggest that genotype-induced changes in 5-HT_{1A} receptor expression affect the structure of brain networks implicated in mood and cognitive function, particularly in anxiety.

Genetic risk: animal models

To test the importance of transcriptional mechanisms in the effects of gene polymorphisms, animal models have been used.[69] Ideally, knockin of the specific polymorphism provides an unequivocal validation of the behavioural effect of that polymorphism (functional phenocopy), as has been done for the *BDNF* Val66Met (rs6265) polymorphism.[70]

HTR1A *rodent models*

Several mouse models support the role of *DEAF1* and 5-HT_{1A} autoreceptors in regulation of the 5-HT system and in major depression and anxiety. Because the sequence of the *DEAF1* site is not highly conserved in mouse and human *HTR1A* genes and mice lack the rs6295 polymorphism,[42] a mouse knockin model of the rs6295 SNP may not be functional. Furthermore, the mouse *HTR1A* gene has 2 *DEAF1* sites, one of which is critical for *DEAF1* repression, and the other seems to also mediate *DEAF1* enhancer activity.[102] Nevertheless, insertion of the human *HTR1A* gene (C and G alleles) in a 5-HT_{1A} knockout mouse background indicates region- and allele-specific differences in *HTR1A* expression, despite restricted *HTR1A* expression in this model.[103] Global knockout of *DEAF1* leads to increased 5-HT_{1A} autoreceptor RNA and protein levels in the raphe, while the PFC had reduced 5-HT_{1A} receptor expression,[42] consistent with PET imaging results in depressed patients[41] and in vitro studies.[39] However, the *DEAF1* knockout mice showed a sex- and test-dependent anxiety phenotype that was more pronounced in males.[104] However, the phenotype was very mild, likely due to a desensitization of G-protein coupling to potassium channels.[104] Specific, inducible knockdown in adult male mice of 5-HT_{1A} autoreceptors by 30% resulted in a stress-resilience phenotype with enhanced and more rapid response to SSRI treatment.[105] Similarly, acute small interfering RNA (siRNA)–induced knockdown of 5-HT_{1A} autoreceptors in male mice induced a rapid antidepressant-like phenotype within days[106] and enhanced response to SSRIs.[107] Surprisingly, induced knockout of 5-HT_{1A} autoreceptors in adult mice (both sexes) resulted in hyperactivation of 5-HT neurotransmission and a paradoxical anxiety response to subacute (9-day) SSRI treatment.[108] Hyperactivation of the 5-HT system may relate to suicidality seen in adolescent patients upon SSRI treatment.[109–111] In contrast, deletion of the repressor *CC2D1A*/Freud-1 in 5-HT neurons of adult mice (both sexes) led to an upregulation of 5-HT_{1A} autoreceptors, and an SSRI-resistant anxiety and depression-like phenotype.[112] Importantly, these effects were dependent on increased 5-HT_{1A} autoreceptors and were not seen in a 5-HT_{1A} autoreceptor-deficient background.[113] Like the Freud-1 knockout mice, knockout in adult 5-HT neurons of MeCP2, an X-linked methyl-binding protein that interacts with and augments *DEAF1* activity, induced 5-HT_{1A} autoreceptors and led to a sex-dependent behavioural phenotype: females had reduced anxiety, whereas males showed increased anxiety and reduced depression-like behaviours.[102] Analogous to the Freud-1 knockout model, behavioural response to atypical antipsychotics in an NMDA hypofunction model of schizophrenia was abolished in *Pet1* knockout mice, which are deficient in 5-HT neurons.[114] Thus, normal function of 5-HT neurons is critical for response to both SSRIs and atypical antipsychotics. These studies suggest that the rs6295-induced upregulation of 5-HT_{1A} autoreceptors drives the increased risk for anxiety- and depression-related phenotypes and confers resistance to SSRI treatment.

HTR1A *genotype, neurodevelopment and neuroplasticity*

Since genotype is present throughout life, the *HTR1A* genotype is likely to exert effects on 5-HT_{1A} transcription throughout development, as indicated by a recent study of *HTR1A* allelic imbalance.[61] In postmortem PFC tissue from healthy controls who were heterozygous for the rs6295 polymorphism, the C allele was associated with increased levels of the corresponding 5-HT_{1A} RNA (rs878567 C allele), both in adult and in fetal (from gestational week 18) tissues.[61] This indicates that the rs6295 polymorphism influences 5-HT_{1A} transcription

throughout life. Several studies have addressed the actions of 5-HT and 5-HT$_{1A}$ receptor dysregulation on behaviour and neurodevelopment using rodent models.[115] In 5-HT$_{1A}$ knockout male mice, conditional rescue of forebrain 5-HT$_{1A}$ heteroreceptors during the early postnatal period, but not in adulthood, rescued the anxiety phenotype of these mice.[116] In contrast, suppression of forebrain 5-HT$_{1A}$ heteroreceptors in adolescent male mice (p35–p50), but not adult male mice, resulted in adulthood depression-like behaviour.[117] On the other hand, lifelong 5-HT$_{1A}$ autoreceptor knockout, or knockdown by 40% in juvenile (p14–p30) male mice, but not adult mice,[105,108] also resulted in adulthood anxiety.[118,119] During these critical periods, 5-HT innervation to cortical and limbic targets is continuing to mature[120,121] and can influence neuroblast migration in these regions.[122] Although the role of 5-HT$_{1A}$ receptors in 5-HT neuronal development remains to be elucidated, there is evidence that hippocampal 5-HT$_{1A}$ heteroreceptors signal to *CREB* to enhance developmental hippocampal synapse formation.[123,124] A similar developmental mechanism could be linked to the above-mentioned correlations between 5-HT$_{1A}$ receptor levels and grey-matter thickness in certain brain regions,[92] which is altered in major depression.[125]

In addition to influencing neurodevelopment, there is evidence that antidepressant-induced signalling through 5-HT$_{1A}$ receptors can affect neuroplasticity in adulthood. Chronic SSRI-induced anti-anxiety, antidepressant and hippocampal neurogenesis actions in male mice are dependent on 5-HT$_{1A}$ heteroreceptors expressed on hippocampal granule cells of the dentate gyrus.[126] The adult-born hippocampal neurons integrate into the dentate gyrus circuitry to inhibit the activity of mature granule cells, conferring stress resilience.[127] There is also evidence that 5-HT$_{1A}$ receptors modulate cortical neuroplasticity in adulthood. For example, in adult rats, chronic fluoxetine induces a rejuvenation of cortical neuroplasticity for ocular dominance, and this effect is mediated by cortical 5-HT$_{1A}$ receptors, signalling through *BDNF* and *ERK1/2*.[128] Thus, even in adulthood, chronic treatment with SSRIs may influence cortical neuroplasticity via 5-HT$_{1A}$ signalling. In this regard, PFC 5-HT$_{1A}$ receptor signalling to phosphatidyl-inositol 3′-kinase, implicated in the acute antidepressant actions of ketamine in mice,[129] is thought to trigger synaptic remodelling.[130] The 5-HT$_{1A}$ signalling mechanisms to neuroplasticity-induced behavioural changes remain incompletely understood, as reviewed recently.[131]

Environmental risk: stress × genotype interaction

In combination with the potential roles of genetic risk factors, a key role for environmental risk factors in mental illness has been shown.[66] The Caspi study[132] highlighted the cooperative interaction between risk genotype (5-HT transporter long polymorphic repeat, 5-HTTLPR) and environment (number of life stress events) associated with major depression, which has been replicated in many[133–136] but not all subsequent studies,[137,138] while a recent study suggests that they are separate, noninteracting risk factors.[139] The 5-HTTLPR risk allele (short, s) or genotype (ss) has been associated with altered hippocampal volume[57] and amygdala–cingulate cortex reactivity to fear-related stimuli[140,141] that can affect response to environmental stress and depression susceptibility. Similarly, work-related stress in a nursing cohort, and major depression in a Japanese cohort were associated with 5-HTT promoter DNA methylation in blood, but no interaction was seen with 5-HTTLPR genotype.[142,143] However, in post-stroke depression an interaction with increased 5-HTT promoter methylation was seen only in people with the 5-HTTLPR ss genotype.[144] Thus, genotype and stress-induced DNA methylation may interact at specific risk gene promoters to predispose people to major depression.[67]

Stress × HTR1A *genotype interaction*

Like 5-HTTLPR, there is evidence that the *HTR1A* promoter polymorphism interacts with stress for susceptibility to anxiety- and depression-related phenotypes. For example, life separation events interacted with both 5-HTTLPR and *HTR1A* rs6295 polymorphisms in panic disorder.[145] Recent stress and the rs6295 G allele increase amygdala reactivity more than either alone.[146] As well, DNA methylation of the C allele has been associated with reduced negative symptom response to antipsychotics in first-episode schizophrenia,[147] which may account for an association with the C allele in 1 study.[148] In agreement, several studies have shown that life stressors, including chronic pain or infection, interact with the rs6295 genotype for anxiety, depression and susceptibility to hospitalization for depression.[51,81,146,149–151] However, in 1 study, although the G allele, childhood or later life stress were each associated with substance abuse, psychiatric hospitalization and suicide, there was no interaction between genotype and trauma in a highly stressed cohort.[61] Similarly, other studies did not find an association between rs6295/stress and depression.[152] An association with suicide or suicide attempt has been seen for rs6295 alone in some but not all studies,[61,153,154] and in other studies the rs6295 genotype has been associated with suicide attempt or suicide only in people with previous trauma.[155,156] The rs6295 *HTR1A* gene polymorphism is one of several SNPs that has been shown to interact with stress exposure in depression susceptibility,[67] each study showing a stress-associated increase in depression frequency for risk alleles. However, as proposed for the 5-HTTLPR, this association may be strongest with persistent or recurrent depression rather than with single-episode depression.[157]

Epigenetic mechanisms: clinical findings and animal models

Environmental stress can affect gene expression through epigenetic changes such as histone modification and DNA methylation.[158,159] Histone acetylation mediates chromatin opening, typically inducing gene activation, while histone deacetylation closes chromatin to mediate gene repression.[160] The DNA methylation of promoters mediates recruitment of methyl-binding proteins to repress gene expression, while methylation of specific repressor sites can reduce gene activation or repression. For example, pups fostered by rats

bred for enhanced maternal care show increased 5-HT activity, leading to reduced stress reactivity in adulthood.[161] This persistent behavioural change involves reduced expression of hippocampal glucocorticoid receptors due to DNA methylation at a specific site in the gene.[162] In humans, early-life abuse is associated with increased methylation of the analogous site in the brains of people who have died by suicide.[163] The effects of 5-HT_{1A} receptors on stress-induced modifications, and of chronic stress on 5-HT_{1A} receptor gene transcription, histone acetylation and DNA methylation are presented in the sections that follow.

Stress and HTR1A *epigenetic regulation: histone acetylation*

The effects of chronic stress on epigenetic modifications of the *HTR1A* gene and depression-like behaviour have been examined in several studies. In addition, several lines of evidence implicate 5-HT_{1A} receptors in modifying the histone acetylation of other genes following stress. The ability of 5-HT_{1A} agonists to promote resilience to restraint stress was associated with increases in hippocampal histone-H3 acetylation and was mimicked by trichostatin-A, an inhibitor of histone deacetylase (HDAC).[164] Similarly, 5-HT_{1A} signalling in visual cortex reduces *HDAC5* levels to trigger neural plasticity in the visual cortex of adult rats with monocular deprivation.[128] Interestingly, *HDAC5* is increased in the PFC following chronic stress, and its inactivation has been implicated in antidepressant response to SSRI, tricyclic antidepressants and ketamine.[165–167] Thus, 5-HT_{1A}-induced signalling to histone-modifying enzymes through unexplored mechanisms may induce resilience to stress-induced depression.

The *HTR1A* gene itself is subject to regulation by histone acetylation. In non-neuronal cells that do not express 5-HT_{1A} receptors, repression of *HTR1A* is HDAC-dependent. In contrast, in neuronal cells that do express the receptor, 5-HT_{1A} receptor gene repression is at least partly HDAC-independent.[168,169] In particular, the repressor Freud-1 assembles different *BRG1* chromatin remodelling complexes in non-neuronal versus neuronal cells to mediate HDAC-dependent and -independent repression, respectively. Neuronal cells show de-repression of the *HTR1A* gene upon depletion of Freud-1 or *BRG1*, while non-neuronal cells are resistant,[169,170] reflecting silencing of 5-HT_{1A} receptor expression in the latter. This reversible regulation of 5-HT_{1A} receptor expression in neurons may account for the dynamic regulation of 5-HT_{1A} autoreceptors by Freud-1 in vivo.[113] Although pharmacological inhibition of HDAC has antidepressant effects, HDAC subtype- or cell-specific inhibition would be needed to specifically target depression-related transcriptional processes.[171]

Stress and HTR1A *epigenetic regulation: DNA methylation*

In addition to altered histone acetylation, chronic stress is correlated with changes in DNA methylation and gene expression and increased risk of major depression or suicide.[159] Several clinical studies have shown alterations in human *HTR1A* gene methylation associated with mental illness and changes in 5-HT_{1A} receptor expression. Increased DNA methylation of the human *HTR1A* promoter in leukocytes has been reported in bipolar depression and schizophrenia.[172] Hypomethylation of the *HTR1A* promoter in lymphocytes from lupus erythematosus patients correlates with increased 5-HT_{1A} expression.[173] Specific methylation of the rs6295 site has been negatively correlated with negative symptom treatment response in schizophrenia.[147] In this regard, *DEAF1* binding to its site is attenuated by DNA methylation,[174] suggesting that increased 5-HT_{1A} autoreceptor expression may be underlying this treatment resistance. More recently, stress-linked hypomethylation in blood cells of a site (CpG668) in the *HTR1A* gene body was correlated with resistance to 8-week escitalopram treatment in treatment-naive depressed patients.[175] Thus, methylation of the 5-HT_{1A} promoter or repressor sites can affect 5-HT_{1A} receptor expression and correlate with schizophrenia and response to atypical antipsychotics. However, the statistical power in many of these trials was not sufficient, and larger studies are needed.

The effect of chronic stress on 5-HT_{1A} receptor promoter methylation and RNA expression has been examined in only one animal model to date. Methylation of 24 CpG sites on the mouse *Htr1a* promoter was quantified following unpredictable chronic mild stress (UCMS) for 9 weeks in male Balb/c mice.[176] Stressed mice showed increased DNA methylation of a single site located within an Sp4 element of the *Htr1a* gene that correlated with increased 5-HT_{1A} RNA levels in both raphe and PFC (Fig. 2). The DNA methylation of this site prevented Sp4-induced repression and could account for the stress-induced increase in 5-HT_{1A} RNA. As shown by transcriptionally upregulating 5-HT_{1A} autoreceptors in the raphe-specific Freud-1 conditional knockout mice,[113] the stress-induced expression of 5-HT_{1A} autoreceptors could mediate the acquisition of depressed behaviour in UCMS mice. Interestingly, in the Freud-1 knockout study, mice were individually housed, a stressor that could contribute to the increase in 5-HT_{1A} autoreceptors and the SSRI-resistant behavioural phenotype. In contrast, chronic treatment of the UCMS mice with the tricyclic antidepressant imipramine reversed the depression-like phenotype, perhaps because imipramine targets additional (e.g., noradrenergic) mechanisms compared with SSRIs. Imipramine also reversed *HTR1A* methylation in both raphe and PFC, but the increase in 5-HT_{1A} RNA was reduced only in the latter. Thus, the stress-induced site-specific DNA methylation appears to alter 5-HT_{1A} receptor expression by inhibiting transcription factor (Sp4) binding, and is reversible upon chronic imipramine treatment.[176] However, additional mechanisms maintained the stress-induced upregulation of 5-HT_{1A} autoreceptors in imipramine-treated mice that could confer a persistent vulnerability to relapse. In this regard, antidepressant-naive depressed participants and remitted depressed participants (off medication) both had elevated 5-HT_{1A} binding compared with controls,[23,177] suggesting increased 5-HT_{1A} expression as a trait or scar (residual characteristic) of persistent depression vulnerability.

Since the effects of DNA methylation on gene expression are mediated in part by methyl-binding proteins, such as

MeCP2,[178] the role of MeCP2 in the regulation of 5-HT$_{1A}$ receptor expression, 5-HT regulation and behaviour was examined.[103] In addition to methylation-sensitive mechanisms, MeCP2 binds to *DEAF1* and enhances its repressor and enhancer activities at the human and mouse 5-HT$_{1A}$ genes (Fig. 2). In mice lacking MeCP2 in adult 5-HT neurons, 5-HT$_{1A}$ autoreceptors were upregulated, indicating that MeCP2 plays a key role to repress 5-HT$_{1A}$ autoreceptor expression. Interestingly, these mice showed a sex-dependent anxiety–depression phenotype, suggesting additional sex-dependent actions of MeCP2 in 5-HT neurons.[103]

Epigenetic regulation of the 5-HT$_{1A}$ receptor may be synergistic with genotype-dependent regulation. In rs6295 heterozygous healthy human fetal and adult PFC, 5-HT$_{1A}$ RNA was preferentially transcribed from the C allele,[61] as expected from the enhancer effect of *DEAF1* at the C allele in this tissue.[39] However, in depressed tissue, C- and G-derived RNAs were equal (Fig. 3), suggesting that *DEAF1* or its regulation is attenuated in depression, potentially by DNA methylation.[61] This suggests that epigenetic processes regulated by chronic stress or antidepressant treatment can modify genotype-associated resilience to major depression. However, as a therapeutic strategy, inhibition of DNA methylation is not specific enough.[158] Instead, transient or cell-specific inhibition of DNA methylation could be used to augment responses driven by antidepressants to enhance their effectiveness, although this remains to be tested.

Posttranscriptional regulation of *HTR1A* expression

MicroRNA mechanisms

As suggested, multiple mechanisms — including gene polymorphisms and epigenetic changes — can regulate promoter activity by altering transcription factor binding (Fig. 2). In addition, posttranscriptional mechanisms — including changes in RNA-binding proteins, such as splice factors, and microRNAs (miRNAs) that target the 3′-untranslated region (UTR) — can alter RNA stability to influence gene expression and neurodevelopment.[179] Recently, regulation of RNA stability by miRNAs has been implicated in major depression.[180,181] For example, miR-16 was shown to inhibit 5-HTT expression in vitro in human, mouse and rat cell lines,[182,183] and chronic fluoxetine treatment in mice induced miR-16 in raphe, correlating with downregulated 5-HTT levels in raphe.[183] In 5-HT neurons compared to non-5-HT neurons, miRNA microarray showed that several miRNAs are depleted, including miR-16 and miR-135.[184] Importantly, miR-135a targets conserved elements to reduce both 5-HTT and 5-HT$_{1A}$ receptor RNA levels, and it was upregulated by acute or chronic SSRI or imipramine treatment. Forced overexpression of miR-135a in the 5-HT neurons of adult male mice reduced 5-HTT and 5-HT$_{1A}$ expression and reversed the anxiety and depression phenotypes following social defeat, while knockdown of miR-135a had the opposite effect on nonstressed mice.[184] In these miR-135a mouse models, reductions of both 5-HTT and 5-HT$_{1A}$ autoreceptors could contribute to the increased 5-HT levels and release that correlated with behavioural improvement, as shown in studies modifying 5-HTT or 5-HT$_{1A}$ expression separately.[105,113,185] Importantly, the potential roles for human miR-16 and miR-135a in depression were suggested by reductions in the raphe of brains of people who had died by suicide compared to healthy controls.[184] Furthermore, miR-135a, but not miR-16, was reduced in the blood of depressed patients and was increased by cognitive behavioural therapy but not SSRIs. Several miRNAs are altered in the blood of depressed versus healthy people, and may serve as functional biomarkers for major depression or treatment response.[181] Furthermore, direct targeting of 5-HTT or 5-HT$_{1A}$ using siRNAs may provide a novel and effective form of molecular therapy for major depression involving dysregulation of these proteins or the miRNAs that target them.[186] However, an important caveat to targeting microRNAs is that, like transcription factors, they have multiple gene targets that could result in adverse outcomes; hence, cell-specific targeting would be important.

Alternative splicing

More recently, attention has focused on alternative splicing as another regulator of gene expression in major depression.[187] Alternative splicing is particularly abundant in the developing human brain[188] and is altered in major depression, resulting in altered RNA structure and new protein variants.[187]

Our recent studies, in addition to confirming regulation by miR-135a, showed that the *HTR1A* gene is subject to a novel alternative splicing event that removes the miR-135 site[189] (Fig. 3). This splicing event is surprising, because the *HTR1A* gene was initially characterized as an "intronless" gene.[190–192] However, in the human (but not rodent) *HTR1A* 3′-UTR, we discovered 2 very similar splice variants that are regulated in opposite ways by the brain-enriched splice factors nSR100 (enhances splicing) and *PTBP1* (inhibits splicing; Fig 3).[189] The spliced *HTR1A* RNA variants are extremely stable compared with the unspliced version that is degraded rapidly, consistent with destabilization induced by miR-135.[184] The level of the unspliced form is lower in the PFC than in the hippocampus and raphe, but its expression increases in depression, which would lead to reduced 5-HT$_{1A}$ receptor levels as seen in postmortem PFC tissue from people with depression who died by suicide and in PET imaging studies of depressed people.[193] Importantly, the levels of splice factor nSR100 were reduced in depressed PFC tissue and could account for the reduced level of 5-HT$_{1A}$ splicing.[189] Thus, both splicing and miRNA regulation of the *HTR1A* gene converge to determine *HTR1A* RNA stability, and reductions in both splice factors (nSR100) and miRNAs (miR-135) that occur in major depression could synergistically alter 5-HT$_{1A}$ protein levels (Fig. 3).

In addition to the convergence of splicing and miRNA, genotype may also influence splicing. The *HTR1A* rs878567 SNP is located in the 3′-UTR of the 5-HT$_{1A}$ receptor close to the splice site, and is in strong linkage disequilibrium with the rs6295 promoter polymorphism.[61] The rs878567 polymorphism has been associated with major depression,[46,47]

schizophrenia,[194,195] psychosis[196] and depression after childhood physical abuse.[197] While many of these associations are similar to those for rs6295, the association with schizophrenia and psychosis was not as robust for rs6295. These differences are consistent with different roles for these SNPs in transcription compared to RNA processing of the 5-HT_{1A} receptor gene. Our preliminary data suggest that the rs879567 C allele (linked to the rs6295 C allele) is associated with greater splicing and thus expression of the 5-HT_{1A} RNA, synergistic with the greater *DEAF1*-induced *HTR1A* transcription in the PFC (Fig. 3). This illustrates the potential importance of genotype in determining the extent of RNA splicing and stability, and how these posttranscriptional processes may be synergistic (or antagonistic) with linked genotypes that affect transcriptional activity.

Recently, the largest genome-wide association study for major depression identified 2 SNPs with genome-wide significance located in the *RBFOX1* gene, a regulator of gene splicing.[198] *RBFOX1* sites are generally located in introns 200 to 300 bp from the splice site, and *RBFOX1* regulates splicing in the nervous system by combining with brain-specific splice factors.[199] It is antagonized by *PTBP1*, which is reduced in the PFC in major depression.[189] Interestingly, in the human *HTR1A* intron there is an *RBFOX1* site (TGCATG) located ~270 bp from the splice acceptor site, suggesting its role in 5-HT_{1A} RNA splicing or regulation, in combination with nSR100 and *PTBP1* in major depression. These converging lines of evidence highlight the potential importance of alterations in splice factor expression to modify alternative splicing and gene expression, resulting in susceptibility to major depression.

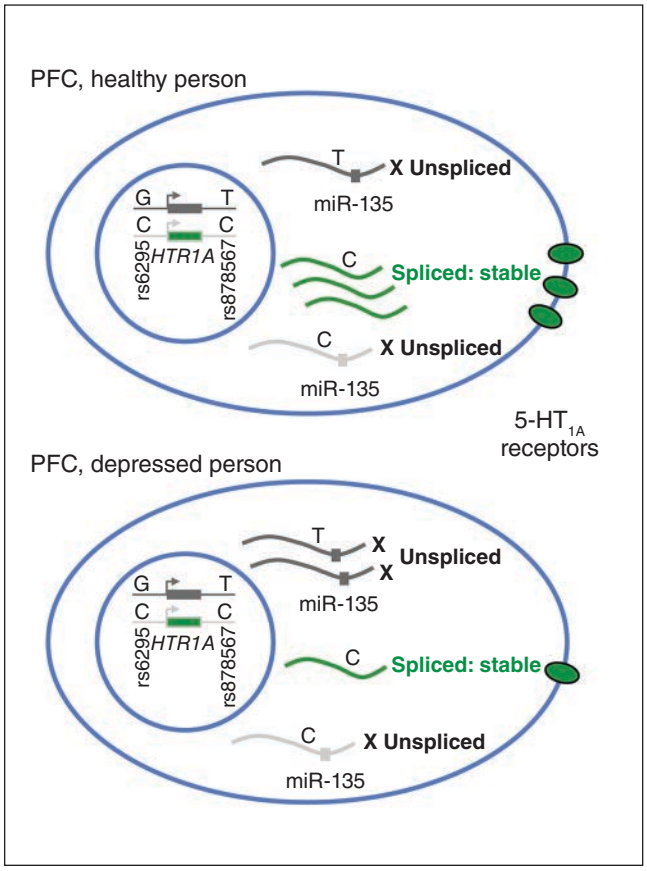

Fig. 3: Model of the effects of genotype on the regulation of 5-HT_{1A} receptor expression by promoters and the 3′-untranslated region. Shown is a model of a neuron in the PFC of a healthy or depressed person, with the most abundant genotypes of the *HTR1A* gene shown in the cell nucleus. Transcription of the rs6295 G allele results in RNA containing the rs878567 T allele and reduced splicing, while transcription of the C allele results in enhanced splicing to stabilize the RNA and increase the translation of 5-HT_{1A} receptors. In the PFC of healthy people, the C allele is favoured, while in the PFC of depressed people they are equal, reducing splicing and 5-HT_{1A} expression. 5-HT = serotonin; PFC = prefrontal cortex.

Conclusion

In summary, the 5-HT_{1A} receptor gene illustrates the multilevel gene transcription and RNA regulatory mechanisms that determine protein expression levels. Alterations in these mechanisms combine to change protein expression and can be influenced by genotype (polymorphisms in both promoter, introns and UTR) and stress/environment (leading to epigenetic changes such as histone acetylation and DNA methylation). Furthermore, changes in the upstream regulators (transcription factors, methyl-binding proteins, splice factors, miRNAs) can have a broad influence on the expression of many genes in a cell, a subset of which seem to more strongly confer risk for mental illness and provide diagnostic or prognostic markers. For example, recent evidence suggests that in some cases blood miRNA (including miR-135) can be used as a marker for major depression and seems to mirror miRNA changes in the brain.[181]

Ultimately, by understanding and targeting or bypassing gene regulatory mechanisms elucidated in animal models, more effective personalized treatments for mental illness may emerge. For example, in depressed patients with the *HTR1A* rs6295 polymorphism and/or showing increased raphe 5-HT_{1A} autoreceptors, as seen in depressed males and at-risk offspring,[200,201] a strategy to block these receptors (e.g., using SSRI with pindolol or vortioxetine), or bypass presynaptic 5-HT by directly targeting postsynaptic 5-HT_{1A} receptors or by targeting other monoamines (e.g., noradrenaline, using SNRIs, tricyclic antidepressants) may be more efficient than SSRI treatment alone.[11] In the future, directly targeting the 5-HT_{1A} autoreceptor using intranasal 5-HT_{1A} siRNA conjugated to SSRI for raphe targeting could be used for knockdown 5-HT_{1A} receptor RNA.[186] One can envisage screening patients' blood samples for depression-related miRNAs and then targeting those brain miRNAs using intranasal therapeutics.[181] These strategies have been tested in animal models, and could be applied to human depression. The evidence from animal models supports a knowledge-based approach to use biomarkers such as genotype, miRNA, receptor or brain imaging, to interrogate the molecular, genetic and cellular mechanisms underlying major depression. With this understanding, personalized strategies to target the underlying causes could be applied for more rapid and effective treatment.

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