5-HT1A Receptors, Gene Repression, and Depression: Guilt by Association
Paul R. Albert and Sylvie Lemonde
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What is This?
Serotonin and Depression

Major depressive disorder (MDD, major or unipolar depression) represents an important clinical problem that has a lifetime risk of between 15% and 20% of the general population, with women having twice the prevalence as men (Doris and others 1999; Fava and Kendler 2000). Additionally, suicide rates can be as high as 15% in patients with a history of severe depressive episodes. Major depression is becoming more prevalent and is predicted to rise within 20 years from the fourth to the second leading cause of global burden of disease (Greden 2001; World Health Organization 2001).

Depression appears to result in part from decreased activity of the serotonin system (Blier and de Montigny 1999; Lesch and Heils 2000). Additionally, suicide rates can be as high as 15% in patients with a history of severe depressive episodes. Major depression is becoming more prevalent and is predicted to rise within 20 years from the fourth to the second leading cause of global burden of disease (Greden 2001; World Health Organization 2001).

Depression appears to result in part from decreased activity of the serotonin system (Blier and de Montigny 1999; Lesch and Heils 2000; Veenstra-VanderWeele and others 2000). The brain serotonin system projects widely throughout the cortex and limbic systems, and 5-HT neurotransmission is believed to play a major role in the control of mood and behavior (Törk 1990; Jacobs and Azmitia 1992; Barnes and Sharp 1999). The synthesis of serotonin is regulated by the level of precursor tryptophan and by the activity of tryptophan hydroxylase (TPH), especially TPH2, which is the rate-limiting enzyme in the brain (Walther and others 2003). Following its release, serotonin action is terminated by reuptake via the 5-HT transporter (5-HTT) and subsequent degradation by monoamine oxidase (MAO). There are 15 known mammalian 5-HT receptor genes (5-HT1A/B/D/E, 5-HT2A/B/C, 5-HT3A/B and 5-HT3C/D/E, 5-HT4, 5-HT5A/B, 5-HT6, 5-HT7) some of which encode additional receptor variants that mediate serotonin actions in the brain as postsynaptic receptors on target neurons (Hoyer and Martin 1997; Barnes and Sharp 1999; Lesch and others 2003). One of the most abundant subtypes expressed in the mammalian brain is the 5-HT1A receptor, which is an intronless gene located on human chromosome 5q11.2-13 (HTR1A) that encodes a single receptor isoform (Albert and others 1990). The 5-HT1A receptor is present on both pyramidal cells and interneurons of the cortex and hippocampus (Aznar and others 2003) and in the septum, amygdala, and hypothalamus. In addition to being widely expressed as a postsynaptic receptor, the 5-HT1A is the major somatodendritic autoreceptor on serotonergic raphe neurons (Sotelo and others 1990; Riad and others 2000). The neuronal 5-HT1A receptor (pre- and postsynaptic) signals via coupling of Gi/Go proteins to inhibit cAMP formation, inactivate calcium channels, and activate potassium channels (Barnes and Sharp 1999) (Fig. 1). Although negative results were reported for 5-HT1A-mediated inhibition of cAMP in raphe membranes (Clarke and others 1996), this probably reflects the low...
The 5-HT1A receptor plays an inhibitory role in postsynaptic projections to the raphe (Hajos and others 1999; Gobbi and others 2001; Mannoury la Cour and others 2001). Desensitization of 5-HT1A autoreceptors disinhibits the serotonergic action potential firing rate, and 5-HT release that correlates with improvement in depressed symptoms. Consistent with negative regulation by 5-HT1A autoreceptors, in 5-HT1A−/− mice, fluoxetine immediately increases 5-HT release to a greater extent than in wild-type animals (He and others 2001; Parsons and others 2001). Desensitization of 5-HT1A autoreceptors is a powerful regulator of both pre- and postsynaptic neurotransmission in the serotonin system.

In support of a role for decreased 5-HT neurotransmission in predisposition to depression, acute tryptophan depletion, which transiently reduces 5-HT synthesis by depleting the precursor tryptophan, induces relapse in 50% to 80% of depressed patients and induces mood lowering in normal subjects (Miller and others 1992; Young 1993; Moore and others 2000). Furthermore, most antidepressants, including serotonin-specific reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs), are thought to act in part by enhancing serotonergic neurotransmission. Pharmacological inhibition of the 5-HT transporter (5-HTT) using SSRIs is effective in clinical treatment of depression, anxiety, obsessive-compulsive disorders, bulimia, and other mood disorders (Charney and others 1990; Pineyro and Blier 1999; Coyle and Duman 2003). SSRIs rapidly enter the brain and block 5-HT reuptake within minutes and should immediately increase 5-HT neurotransmission; however, chronic treatment for at least 2 to 3 weeks is required for clinical efficacy. This delay in antidepressant action may be due to negative feedback regulation via serotonin-1A (5-HT1A) receptors present on serotonin neuron cell bodies and dendrites (autoreceptors) that inhibit raphe activity upon local release of 5-HT within the raphe nuclei (Albert and others 1996; Pineyro and Blier 1999) (Fig. 1). Upon treatment with SSRIs or other antidepressants, recurrent activation of the 5-HT1A autoreceptor occurs to reduce raphe neuronal firing and reduce 5-HT release (Stahl 1998; Blier and de Montigny 1999; Hjorth and others 2000), essentially compensating for any increase in 5-HT that would be produced by the SSRI treatment. The 2- to 3-week latency for antidepressant actions suggests that long-term adaptive changes in the 5-HT system, both pre- and postsynaptically, must occur before SSRIs can ameliorate depressed behavior.

Adaptive Changes Following Chronic Antidepressant Treatment

Selective desensitization of 5-HT1A autoreceptors is postulated to be a key adaptive change that permits antidepressant actions (Fig. 1). After 2 to 3 weeks of SSRI treatment, there is an internalization and loss of 5-HT1A autoreceptors (Hervas and others 2001; Riad and others 2000), whereas postsynaptic receptors remain present. Similarly, in 5-HTT−/− mice, there is a desensitization of 5-HT1A autoreceptors without affecting the responsiveness of postsynaptic receptors (Fabre and others 2000; Gobbi and others 2001; Mannoury la Cour and others 2001). Desensitization of 5-HT1A autoreceptors disinhibits 5-HT neuronal firing, leading to enhanced 5-HT release that correlates with improvement in depressed symptoms. The net effect of 5-HT1A signaling is to reduce neuronal firing rate, neurotransmitter release, and protein kinase activation. There is a second, indirect negative feedback pathway that involves 5-HT1A-induced inhibition of cortical neurons that send excitatory glutamatergic projections to the raphe (Hajos and others 1999; Celada and others 2001; Martin-Ruiz and others 2001). The 5-HT1A receptor plays an inhibitory role in postsynaptic cells and is often localized at the axon hillock, the critical site of action potential initiation (Fig. 2). Hence abundance of 5-HT1A-positive cells in this preparation (less than 5%).

Fig. 1. Adaptive changes in 5-HT1A receptors following chronic SSRI treatment. The 5-HT1A receptor signals via pertussis toxin-sensitive G proteins GiqGs to mediate inhibitory actions in neurons including 1) inhibition of adenyl cyclase (AC) to decrease cAMP levels, 2) opening of potassium channels (K+) to hyperpolarize the membrane potential (Vm) and reduce firing rate, and 3) inhibition of N-type or L-type calcium channels to decrease intracellular calcium concentration ([Ca++]). These inhibitory signaling pathways are observed for both presynaptic 5-HT1A autoreceptors on 5-HT neuron cell bodies and dendrites and postsynaptic 5-HT1A receptors on nonserotonergic neurons (yellow dots). In addition, other 5-HT receptors are expressed postsynaptically (colored dots). Before antidepressant treatment, 5-HT1A autoreceptors regulate the firing rate (spikes) and 5-HT release (black specks). Acutely, SSRI antidepressants inhibit 5-HTT (red Xs) the 5-HT transporter (orange arrows) and also reduce serotonergic firing (red arrow) by augmenting 5-HT levels (red specks) at the cell body, leading to activation of 5-HT1A autoreceptors. After 3 weeks, a reduction in the number or signaling of 5-HT1A autoreceptors via homologous desensitization is observed: this disinhibits the serotonergic neuron, enhancing action potential firing rate and releasing more 5-HT, correlating with clinical amelioration of depression.
tors is observed in rodents upon chronic treatment with antidepressants as diverse as MAOIs and TCAs (that target monoamine systems) (Gur, Lifschytz, and others 2002); electroconvulsive therapy and transcranial magnetic stimulation (TMS) (Gur and others 2000; Gur, Dremencov, and others 2002) (that target multiple systems and are effective in SSRI/TCA resistant patients); and even novel antidepressant NK-1 receptor antagonist MK-869, that inhibits 5-HT1A autoreceptor function (L Santarelli and others 2001). Alone, 5-HT1A-selective ligands (such as buspirone, ipsapirone) are weak antidepressants. However, pindolol, by selectively targeting 5-HT1A autoreceptors, can accelerate and potentiate SSRI action (Artigas and others 1996; Blier and Ward 2003). Although pindolol augmentation is not always effective, imaging studies suggest that at typical clinical doses the 5-HT1A autoreceptor is not blocked by pindolol (Rabiner and others 2000; Martinez and others 2001). Because pindolol has partial agonist activity on raphe neuronal firing (Haddjeri and others 1999; Arborelius and others 2000), it may enhance 5-HT1A receptor desensitization in addition to inhibiting 5-HT-induced autoreceptor activation (Artigas and others 2001). Taken together, these studies indicate that the 5-HT1A autoreceptor prevents SSRI action to enhance 5-HT neurotransmission and must be desensitized to permit antidepressant action. The common property of multiple antidepressant treatments to desensitize 5-HT1A autoreceptors suggests that this is an important regulatory mechanism in depression. The mechanism for preferential desensitization of presynaptic 5-HT1A receptors remains unclear but may involve differences in 5-HT1A receptor reserve or regulation in pre- versus postsynaptic neurons (Shen and others 2002). This is consistent
with the serotonin hypothesis that postulates that adaptive changes in the serotonin system are the primary lesions in depression but that lead to numerous secondary changes in other neurotransmitter systems. However, enhancement of 5-HT neurotransmission may not act immediately and may require additional postsynaptic adaptive changes such as recruitment of neurotrophin signaling, synaptic remodeling, or neurogenesis (Nestler and others 2002; Duman 2004).

Altered Regulation of 5-HT1A Receptors in Depression

Adaptive Mechanisms for 5-HT1A Receptor Desensitization

Several processes of agonist-induced receptor desensitization (Fig. 3) could underlie the adaptive mechanisms that regulate 5-HT1A autoreceptors and serotonin function following chronic antidepressant treatment (Albert and others 1996; Raymond and others 1999). Acutely following activation by agonist (serotonin), receptor uncoupling occurs within seconds. Uncoupling involves agonist-induced phosphorylation by G-protein-coupled receptor kinases (GRK) or second messenger kinases (PKC, PKA) and prevents receptor signaling through G-proteins, but it does not remove the receptor from the plasma membrane and is rapidly reversible upon removal of agonist. This is followed by receptor internalization, which occurs within seconds to minutes and leads to removal of the receptor from the plasma membrane into clathrin-coated vesicles (Ferguson 2001; Shenoy and Lefkowitz 2003). Receptor internalization is initiated by agonist-induced receptor phosphorylation, recruitment of β-arrestins, and assembly of clathrin-coated pits leading to receptor internalization. It is important to note that while removed from external stimuli, the internalized receptor can initiate new signaling pathways such as coupling to mitogen-activated protein kinase (MAPK) and hence is not necessarily inactive and could represent an acute initiator of adaptive changes. Receptor internalization can be rapidly reversible depending on the affinity of the phosphorylated receptor for β-arrestin (Ferguson 2001). Finally, upon sustained agonist treatment for hours, the internalized receptor becomes targeted for degradation by an incompletely understood process that may involve monoubiquitinylation of receptor or associated proteins (e.g., β-arrestin) to target the vesicles to fuse with lysosomes resulting in receptor degradation (Shenoy and Lefkowitz 2003).

The turnover time for 5-HT1A autoreceptors in vivo has been estimated at 2 to 3 days following cessation of its transcription (Gross and others 2002). Hence, the above mechanisms of desensitization appear to be too rapid to explain adaptive changes in 5-HT1A autoreceptor number that typically occur over a period of weeks as observed following antidepressant treatment. However, changes in gene expression and the synthesis of new receptors can occur over a prolonged time course and, once initiated, can persist for the lifetime of the organism. Hence we hypothesized that alterations in 5-HT1A receptor gene transcription could be a contributing factor to the delayed effect of antidepressant treatment.

Altered Basal Expression of 5-HT1A Receptors in Mental Illness

The above results suggest that 5-HT1A autoreceptors become desensitized following chronic antidepressant treatment to disinhibit raphe firing and enhance 5-HT neurotransmission (Fig. 1). As a corollary, we hypothesized that alterations in the basal expression of 5-HT1A autoreceptors could predispose the individual to depres-
sion or other mental illnesses that are thought to involve dysregulation of the 5-HT system (Fig. 2). The evidence for increased levels of 5-HT1A autoreceptors in human depression and suicide is from studies of postmortem brains from depressed suicide victims (Stockmeier and others 1998). Compared to nonsuicide tissue, there was a specific upregulation of 5-HT1A autoreceptors in the raphe area, with no change in postsynaptic 5-HT1A receptor sites (Fig. 2). Another study has shown a decrease in raphe 5-HT1A receptor density in the mesencephalon; however, this group found that the total number of 5-HTT- and 5-HT1A-positive (5-HT) dorsal raphe neurons is decreased by 40% with little change in the number of the 5-HT1A receptor/cell (Aranzo and others 2001). Similarly, a decrease in 5-HTT-positive projections in the prefrontal cortex was found in postmortem tissues of depressed suicide victims (Austin and others 2002). A decrease in 5-HT neurons and their projections might lead to decreased 5-HT release, a similar outcome as predicted for increased 5-HT1A autoreceptors (Fig. 2). However, there was an increase in TPH-positive cells in the dorsal raphe of depressed suicides (Underwood and others 1999), suggesting a compensatory upregulation of TPH. Thus, an independent marker of 5-HT neurons such as PET-1 (Hendricks and others 1999) is needed to verify that changes in neuron number occur and not simply change in expression levels. Indirect evidence suggests that embryonic activity of 5-HT1A receptors may negatively regulate the number and differentiation of 5-HT neurons (Runmajoege and others 2004), suggesting a role for 5-HT1A autoreceptors in decreased 5-HT neuron number in depressed subjects. In the hippocampus and dorsolateral prefrontal cortex, a decrease in postsynaptic 5-HT1A RNA was observed in postmortem studies of major depression (Lopez-Figueroa and others 2004), consistent with decreased postsynaptic 5-HT1A signaling observed in depressed suicide tissue (Hsiung and others 2003). These reductions in 5-HT1A receptors could reflect decreased cell number in these regions in depression, as described in the next paragraph (Fig. 2). These examples serve to highlight the fact that multiple mechanisms that can reduce 5-HT neurotransmission could contribute to predisposition to depression or suicide.

Several positron emission tomography (PET) imaging studies of human patients with bipolar depression, unipolar (major) depression, and panic disorder have shown a decrease in 5-HT1A receptor density, particularly in the dorsolateral prefrontal cortex (Drevets and others 2000; Sargent and others 2000; Neumeister and others 2004). Oppositely, in schizophrenia there is a specific upregulation of 5-HT1A binding in the prefrontal cortex (Sumiyoshi and others 1996; Burnet and others 1997; Tauscher and others 2002). These changes could be due to alterations in 5-HT1A expression or changes in neuronal number (Fig. 2). Detailed morphometric analyses of the postmortem brain indicate decreased arborization and smaller size of neurons and glia in the prefrontal cortex of depressed subjects (Rajkowska 2000, 2003) that could account for decreased levels of 5-HT1A receptors. Similarly, imaging studies of depressed SSRI responders versus nonresponders indicate increased prefrontal and anterior cingulate cortex glucose metabolic activity (but decreased subgenual cingulated activity [Cg25]) correlates with drug response (Mayberg 2003). Interestingly, psychotherapy appeared to target distinct cortical regions from those modulated by SSRI pharmacotherapy, suggesting distinct mechanisms of action. Reductions in cortical neuron number, size, or receptor levels could result in part from and contribute to impaired cortico-limbic connections (Mayberg 2003) and may be due in part to changes in serotonin, stress/glucocorticoid, or other signaling observed to decrease hippocampal neurogenesis and differentiation (Fig. 2). A recent meta-analysis of 17 separate case-controlled imaging studies has shown an association of decreased hippocampal and amygdala volume and major depression (Campbell and others 2004). Although first-episode depressed patients displayed impaired hippocampal function (memory) compared to controls, hippocampal volume reduction was observed only in patients with multiple episodes of depressive illness, suggesting progressive impairment of hippocampal function in depression (MacQueen and others 2003). Reduction in hippocampal development and activity may cause depression or accentuate the effects of stress and decreases in monoamine neurotransmission that are associated with depression (Lopez and others 1998). In combination with decreased presynaptic activity due to loss of raphe cells or increase in 5-HT1A autoreceptors, serotonergic neurotransmission particularly through 5-HT1A receptors appears to be compromised in depression (Fig. 2).

**Novel Regulators of the 5-HT1A Receptor Gene**

**Basal Regulation of 5-HT1A Receptor Gene Transcription**

To identify genetic mechanisms of 5-HT1A receptor regulation, we first addressed the basal regulatory elements of the rat 5-HT1A receptor gene in rodent neuronal cell lines that we found to express the 5-HT1A receptor endogenously (Charest and others 1993; Storring and others 1999). These included SN-48 cells (Lee and others 1991), a fusion between rat postnatal day 21 septal neurons and mouse neuroblastoma and serotonergic RN46A cells, derived from e13 rat midbrain neurons transformed with a temperature-sensitive SV40 retrovirus (White and others 1994). As shown in the model (Fig. 4), the 5-HT1A receptor gene is composed of a proximal promoter containing highly conserved DNA elements for Sp1/MAZ1 and NF-kB within the initial 1 kb of 5′-sequence (Drewe and others 1996; Tauscher and others 2002). These elements drive transcriptional initiation via multiple TATA-less (for human and mouse 5-HT1A genes) or a TATA-containing site
HT1A receptor gene in receptor-negative nonneuronal elements, FRE, TRE, and RE-1, silence the 5′-in nonneuronal 5-HT1A-negative cells. Thus, three transcriptional regulatory elements in neuronal cells, but no derepression occurred in nonneuronal cells but is present in most neurons (Schoenherr and Anderson 1995). Importantly, Freud-1 was expressed in neuronal cells such as raphe RN46A and SN-48 cells, in addition to nonneuronal cells, and was localized in the nucleus of these cells, consistent with its function as a transcription factor. Overexpression of Freud-1 downregulated 5-HT1A expression in both raphe and nonneuronal myoblast cell lines (although more robustly in raphe, Fig. 6A), whereas antisense to Freud-1 derepressed the gene only in raphe cells (Fig. 6B) resulting in an upregulation of 5-HT1A receptor protein (Fig. 6C). In addition, Freud-1 protein was colocalized with 5-HT1A receptors in the hippocampus, cortex, and hypothalamus. Thus, Freud-1 is a neuronal repressor that acts at the DRE to regulate the basal expression of the 5-HT1A receptor gene. In nonneuronal cells, additional repressors (e.g., REST/NRSF), which represses neuronal gene primarily in nonneuronal cells and is bound by the pan-neuronal repressor CAMK-dependent protein kinase, NRE = NF-κB-response element.

**Freud-1: Repressor of 5-HT1A Gene Expression in Neurons**

Because the sequence of the DRE did not correspond well to known repressor elements, we used the DRE as a target sequence to clone proteins that bind to it using the yeast one-hybrid system (Fig. 5). A screen of 10^5 clones of a mouse brain cDNA library revealed two reproducible positive clones that encoded the same protein, which we named Freud-1 (FRE Under Dual repression binding protein-1) (Ou and others 2003). Freud-1 is a novel transcription factor that binds specifically to the FRE and represses 5-HT1A gene transcription through this element. Importantly, Freud-1 was expressed in neuronal cells such as raphe RN46A and SN-48 cells, in addition to nonneuronal cells, and was localized in the nucleus of these cells, consistent with its function as a transcription factor.
Fig. 6. Freud-1 inhibits 5-HT1A transcriptional activity and receptor expression. RN46A or L6 cells were transiently co-transfected with –1590 5-HT1A promoter–luciferase reporter construct and with vector (Control), Freud-1 (A), or antisense (B) expression vector (2 µg for RN46A and 4 µg for L6), and 5-HT1A transcriptional activity was normalized to Control (1.0). Freud-1 protein expression was detected by Western blot (above) and in both cell types was increased by twofold with sense Freud-1 and decreased by 50% with antisense Freud-1 cDNA. Reduction of Freud-1 in L6 cells did not derepress 5-HT1A transcription, suggesting that other repressors (e.g., REST) maintain repression (see Fig. 4). C. RN46A cells were transiently transfected with Freud-1 sense or antisense, with ds-Red as a marker for transfected cells. Note that cells transfected with Freud-1 (red) had qualitatively less 5-HT1A staining (green) than cells not transfected (not labeled red), whereas cells transfected with antisense to Freud-1 (red) had greater 5-HT1A staining (green) than nontransfected cells. From Ou and others (2003), with permission.
REST/NRSF) maintain repression of the 5-HT1A receptor gene in the absence of Freud-1/FRE function (Fig. 4).

The structure of Freud-1 (Fig. 7) is consistent with its function as a transcription factor: it has a basic isoelectric point, a putative DNA-binding helix-loop-helix (HLH) domain. Freud-1 homologues from Drosophila and C. elegans to man have conserved repeats of a novel DM14 domain of unknown function. In addition, Freud-1 contains a putative C2 calcium/phospholipid-binding domain, homologous to the PKC C2/Ca1B domains. The HLH and C2 domains are highly conserved among Freud-1 homologues and are closely adjacent, and the C2 domain contributes in part to DNA binding and repression activity of Freud-1.

Other Freud-1-related sequences have been identified in the GenBank (Fig. 7). In particular, a second related gene (named Freud-2) is present in both human and mouse genome. This second form is highly conserved in the HLH and C2 domains but has three DM14 domains and is less conserved in the N-terminal region containing these domains. In addition, both human and mouse Freud-1 and Freud-2 have long isoforms. Freud-1 or -2 cDNAs encoding longer forms of Freud-1 with a 300-amino acid N-terminal extension are reported in human and mouse databases (accession numbers NP_060191 and AAH27028). By Western blot, we have detected the presence of an approximately 110-kDa protein that could correspond to this longer form of Freud-1, and we are currently examining the function of Freud-2 and the long isoforms.

Despite the presence of a conserved C2 domain, calcium alone does not affect Freud-1 function. However, calcium/calmodulin-dependent protein kinase (CAMK) inhibited Freud-1-induced repression of the 5-HT1A receptor gene (Ou and others 2003). In transcription assays, we found that Freud-1/FRE-mediated repression was inhibited by depolarization- or ionophore-induced calcium increase, which was reversed by CAM or CAMK inhibitors. Thus, Freud-1 can be blocked by calcium-dependent signaling, either via direct phosphorylation of Freud-1 or indirectly via phosphorylation of a coregulator. In addition to regulation by phosphorylation, a human Freud-1 homologue (NP_060191) has been shown to mildly upregulate NF-κB-like activity in HEK-293 cells (Matsuda and others 2003). Because NF-κB upregulates 5-HT1A gene transcription (Wissink and...
others 2000; Abdouh and others 2001), Freud-1-mediated NF-κB induction could feed back to reverse Freud-1-mediated repression of the 5-HT1A receptor.

Like REST/NRFSF, it is likely that Freud-1 recruits corepressors to mediate gene repression. Little is known regarding the mechanism of Freud-1-mediated repression. We have shown that the Freud-1 protein can mediate repression at heterologous Gal4 element when tethered to Gal4-DNA binding domain, suggesting that Freud-1 itself has repressor activity (Lemone and others 2004). In addition, unlike the HDAC-dependent repression of REST/NRFSF, Freud-1-mediated repression is HDAC-independent. Freud-1 contains two potential C-terminal binding protein (CtBP) sites and may recruit the co-repressor CtBP, which can act in an HDAC-dependent or -independent manner (Chinnadurai 2002). Alternately, other mechanisms such as recruitment of MeCP2 or other methylation dependent repressors may mediate repression by Freud (Yu and others 2000; Fuks and others 2003).

In summary, we identified a general repressor region that inhibits 5-HT1A expression in neurons, and a novel transcriptional repressor (Freud-1) that mediates much of this repression (Ou and others 2003). The question arises whether these elements play a role in vivo in human depressed patients. For example, alterations in the level of Freud-1 expression or activation of Freud-1 by decreased intracellular calcium levels (e.g., following 5-HT1A receptor activation) would downregulate the expression of 5-HT1A receptors. Further studies are required to address the role of Freud-1 in depression or antidepressant action. We have addressed further the presence of genetic alterations in the 5-HT1A promoter and conducted association studies in depressed patients (Lemone and others 2003), as discussed below.

**Gene Association Studies in Depression**

**Linkage versus Association Studies**

Depression is a complex disorder resulting from the interaction between multiple environmental and genetic factors (Champoux and others 2002; Caspi and others 2003). Despite evidence of a genetic component for MDD in twin studies, with heritability of between 31% and 42% (Hyman 2000), specific genetic contributions to major depression remain to be characterized. Linkage analysis has been difficult because depression is likely to involve multiple genetic loci (Berrettini 2000; Johansson and others 2001; Segurado and others 2003). In an alternate approach, polymorphisms in candidate genes have been associated with traits or illness (Hamer 2002). However, association studies in mood disorders are often not replicated owing to heterogeneity of the disorder, varying frequencies of alleles in different populations, and small odds ratios due in part to the probable multigenic contribution to susceptibility (Fava and Kendler 2000). In an alternate approach, researchers have attempted to correlate traits of mental disorders with polymorphisms identified in candidate genes involved in the expression of various components of the neurochemical systems associated with the pathophysiology of depression or suicide (Veenstra-VanderWeele and others 2000; Arango and others 2003; Reif and Lesch 2003). Recent findings of associations between specific gene polymorphisms in monoamine transporters, receptors, and biosynthetic enzymes with the predisposition, treatment response, and endophenotypes of mood disorders such as depression or anxiety suggest the importance of genetic changes in the etiology, treatment, and progression of these diseases. However, an important limitation of association studies is replication in diverse population samples. An illustrative example is the studies of TPH1 polymorphisms where association results were inconsistent. Because TPH2, not TPH1, is present in the brain (Walther and others 2003), one reason may be that peripheral alterations in TPH have a lesser contribution to brain 5-HT levels and mood disorders than alterations in TPH2. Association studies of TPH2 polymorphisms in mental illness have begun to appear and may represent more reproducible avenues of research.

**Association Studies for Depression: 5HTTLPR**

Molecular variation in genes of the serotonin system has been associated with various mental disorders (Veenstra-VanderWeele and others 2000), but functional polymorphisms are rare. The long and short variants of the 44-bp 5-HTT long polymorphic repeat (5-HTTLP) are prevalent in the general population and influence the level of 5-HTT gene transcription. The short 5-HTT allele was associated with lower 5-HTT expression in transformed normal subjects (Hariri and others 2002). Another large study (> 1000 subjects) showed that the 5-HTTLP short allele is associated with increased rates of depression and suicidality following early life maltreatment (Casp and others 2003), indicating the importance of interaction between the serotonin system and the stress axis (Fig. 2). By analogy, in nursery-reared versus mother-reared rhesus monkeys, the short 5-HTT allele conferred increased distress and disorientation (Champoux and others 2002). Depressed subjects with short alleles of the 5-HTT promoter display increased susceptibility to depressive symptoms following tryptophan depletion (Moreno and others 2002; Neumeister and others 2002). Oppositely, the long allele is associated with greater reduction in hippocampal volume in major depression (Frodl and others 2004), raising the possibility that hippocampal volume change may be an effect rather than a cause of depression. The 5-HTTLP short allele is associated with decreased transcription of the 5-HTT gene that would be predicted to produce depletion of 5-HT levels but increased 5-HT neurotransmission (due to reduced 5-HT clearance from the synaptic cleft) as observed in 5-HTT−/− mice (Holmes and others 2003).
However, adaptive changes in 5-HT1A autoreceptors and other mechanisms could compensate for the 5-HTTLPR allele, and multiple genetic and environmental interactions ultimately determine the level of 5-HT neurotransmission. Thus, the 5-HTTLPR provides an important benchmark for genetic association studies in depression and related mental illnesses. Although the importance of these studies should not be exaggerated, the effect of this polymorphism on 5-HTT levels in the brain and the exact transcriptional regulatory mechanisms involved remain unclear. For example, the 5-HTTLPR displays repressor activity in RN46A cells but enhancer activity in nonneuronal cell lines (Sakai and others 2002), suggesting that its regulation in the brain may differ from nonneuronal regulation in lymphoblasts. Thus, further studies of the influence of the 5-HTTLPR on 5-HTT expression in cells and in vivo are necessary.

Association Studies for Depression: 5-HT1A Receptor

Several rare single nucleotide polymorphisms (SNPs) have been described for the 5-HT1A receptor gene (Erdmann and others 1995; Kawanishi and others 1998). Polymorphisms in the N-terminal domain of the 5-HT1A receptor coding sequence have been shown to alter the desensitization (Gly22Ser mutant [Rotondo and others 1997]) or 5-HT-induced response of the receptor (Ala50Val mutant [Del Tredici and others 2004]). However, these mutations have a low frequency in the general population (< 2%), and no association with mental illness was shown.

Because of the importance of the repressor region in regulating receptor 5-HT1A expression in neurons, we reasoned that the repressor region might contain polymorphisms that could lead to upregulation of the 5-HT1A autoreceptor to decrease serotonin neurotransmission and that may be associated with mental illness. Accordingly, we performed PCR analysis of the repressor region of the 5-HT1A gene on DNA extracted from human blood samples from 129 depressed or 134 normal subjects (Lemonde and others 2003). Although no polymorphism was identified proximal to the DRE or RE-1 sequences, we identified a single nucleotide C/G change at −1019, which was reported initially as −1018 (Wu and Comings 1999). In our study, the 5-HT1A homozygous G(−1019) allele was at least twofold more frequent in the depressed cohort than matched control subjects, and subsequently we showed this allele was fourfold enriched in 102 completed suicide victims. It is important to note that these associations were found using ethically different populations, and mainly males for the suicide study. In addition, the depressed cohort that we investigated was relatively severely depressed (HAM-D17 score of 24 ± 3). Another study in a Spanish cohort depressed patients failed to find a similar relationship (Arias and others 2002, 2003). This discrepancy might be explained by differences in frequency of the G(−1019) allele in control populations, different population sampling, and possibly by a sizeable difference in sex distribution between patient group and control group used in this study (74% females in the patient group vs. 47% in the controls). Thus, further studies are required to replicate the association of the C(−1019)G allele with major depression, or perhaps a subtype of major depression. In this regard, preliminary analysis of the depressed group from our previous study (Lemonde and others 2003) shows a significant association of the G(−1019) allele with reduced response to antidepressants (Lemonde and others, unpublished observations).

Since our original studies, two additional association studies of the C(−1019)G 5-HT1A polymorphism have appeared. In one study, the G/G allele was associated with the endophenotypes of depression and anxiety on the NEO rating scale for neuroticism in 284 normal subjects (Strobel and others 2003). This result suggests that in normal subjects the G(−1019) allele is associated with a predisposition to a depressed phenotype, indirectly supporting our initial finding that this allele is associated with major depression. Another study showed an association of the 5-HT1A G(−1019) allele with panic disorder with agoraphobia (a more severe phenotype) in 134 female subjects and controls (Rothe and others 2004). Like depression, panic disorder may be due to an imbalance of the 5-HT system and is treated with SSRIs (Blier and de Montigny 1999). These initial reports of an association of G(−1019) with depression and panic disorder could reflect a comorbidity with increased risk of completed suicide, for which we found the strongest association with the G(−1019) allele (Lemonde and others 2003).

C(-1019)G: A Functional 5-HT1A Polymorphism

Because the 5-HT1A C(−1019)G polymorphism is located in a transcriptional regulatory region and the sequence was within a 26-bp palindrome, a possible site of protein-DNA interactions, we addressed whether nuclear proteins from raphe cells bound to the 26-bp palindrome sequence surrounding the polymorphism. We identified a nuclear protein complex in serotonergic neuron derived cells that binds to the C-allele but not the G-allele of palindrome DNA sequence (26-bp). The identity of these proteins was determined using yeast one-hybrid cloning (Fig. 5), and transcriptional factors NUDR/Deaf-1 and Hes5 were shown to bind to and transactivate the C(−1019) allele specifically. In transcriptional reporter assays, NUDR and Hes5 repressed the transcription activity of the C(−1019) allele of the 5-HT1A promoter (Fig. 8A), and this transcriptional repression is dramatically reduced in the presence of the G(−1019) allele, although Hes5 was less sensitive than NUDR (Fig 8B). Furthermore, NUDR expression in raphe RN46A cells decreased levels of endogenous 5-HT1A mRNA, protein, and binding sites (Fig. 9). Using immunocytochemistry of adult rat brain, NUDR and 5-HT1A receptors were colocalized with 5-HT1A receptors and 5-HT in neurons of the raphe nuclei, but also in postsynaptic neurons in the hippocampus and the frontal cortex (Lemonde and others 2003), whereas Hes5 is
mainly expressed in early development (Kageyama and Ohtsuka 1999). NUDR/Deaf-1 contains a SAND domain with a conserved KDWK motif that mediates DNA binding and gene repression and binds to an inverted TTCG element (Bottomley and others 2001) in the 5-HT1A 26-bp palindrome, which is disrupted in the homozygous G(–1019) allele. Although our studies indicate a role for NUDR in regulation of 5-HT1A receptors, NUDR is likely to play multiple roles in the regulation of other genes, in that it is expressed in multiple tissues (Michelson and others 1999). NUDR–/– embryos display neural tube exencephaly at the mid-hindbrain region, resulting in death at birth (Hahm and others 2004), consistent with a role for NUDR in the early formation of midbrain structures that may include serotoninergic raphe nuclei. In addition, NUDR–/– mice display bone abnormalities, suggesting additional roles for NUDR in the periphery. Based on the colocalization of 5-HT1A receptors and NUDR in adult tissue and the greater sensitivity of NUDR to the C(–1019) polymorphism, we suggested that NUDR is the primary regulator at this site, at least in the adult (Fig. 10). However, both NUDR and Hes5 (or other Hes family members) could play a role to regulate 5-HT1A receptors in embryonic development.

Our results suggest a molecular mechanism by which the single nucleotide C(–1019)G polymorphism may regulate 5-HT1A gene expression in vivo by derepression of the 5-HT1A promoter in presynaptic raphe neurons leading to reduced serotonergic neurotransmission (Fig. 10). However, NUDR can repress or enhance transcription, and it enhances proenkephalin gene transcription (Michelson and others 1999). Our preliminary results show that the transcriptional factor NUDR enhances 5-HT1A transcriptional activity in hippocampal and septal neuronal cell lines and that the G(–1019) allele attenuated NUDR enhanced 5-HT1A transcription in postsynaptic cells (Lemonde and others, unpublished data). The net effect of these changes would be a reduction in serotonergic neurotransmission. We hypothesize that specific assays for 5-HT1A receptor function in normal and depressed patients will have a stronger association with major depression than genetic association with the homozygous G(–1019) genotype.

Linking 5-HT1A Genotype to Phenotype

The mechanistic evidence that the C(–1019)G polymorphism is functional fits very well with evidence from postmortem studies suggesting increased presynaptic 5-HT1A binding (Stockmeier and others 1998) and PET findings of decreased postsynaptic 5-HT1A levels in depressed patients (Drevets and others 2000; Sargent and others 2000). However, decreases in midbrain 5-HT1A receptors are observed in bipolar depression and panic disorder patients in PET studies (Drevets and others 1999; Neumeister and others 2004), but this could also reflect decreased 5-HT cell number (Arango and others 2001) or insufficient washout of medication effects to downregulate the 5-HT1A receptor. However, it remains to be determined whether the G(–1019) 5-HT1A allele is associated with increased 5-HT1A receptors in the midbrain of depressed suicide postmortem tissue (Stockmeier and others 1998). Studies in nonmedicated depressed patients may clarify the latter problem. Analogous studies to associate 5-HTTLPR genotypes with 5-HTT levels in the brain have not shown a correlation (Mann and others 2000; Shioe and others 2003). This probably reflects the complexity and variety of regulatory influences and adaptive responses that can determine the level of protein expression measured by PET or in the postmortem brain. In summary, although the 5-
HT1A C(–1019)G polymorphism may be associated with depression and provide a transcriptional model for its etiology, further validation of the genetic association in other cohorts is required, and animal models that could replicate the depressed phenotype need to be developed.

Models for Depression

5-HT1A Animal Models and Anxiety

To address mechanisms of depression and anxiety, animal models can provide important insights. Despite limitations of animal behavioral tests in modeling mental illness in humans (Schechter and Chance 1979), some behavioral models in rodents such as forced swim test or novelty-suppressed feeding are responsive to chronic but not acute antidepressant treatment, providing models of antidepressant response (Santarelli and others 2003; Schramm and others 2001). In three different strains of 5-HT1A–/– mice, increased anxiety-related behavior is observed and is associated with increased serotonergic neurotransmission due to loss of 5-HT1A autoreceptors (Heisler and others 1998; Parks and others 1998; Ramboz and others 1998; He and others 2001; Parsons and others 2001). Importantly, the anxiety behavior of 5-HT1A–/– mice is unresponsive to SSRI but is ameliorated by TCA, indicating the primary role of 5-HT1A autoreceptors in SSRI action (Santarelli and others 2003). Another model with increased anxiety is the neurokinin-1 (NK1) receptor –/– mouse (L Santarelli and others 2001). In the raphe nuclei of NK1R–/– mice, a reduction of 5-HT1A autoreceptor expression was associated with a decreased anxiety phenotype. NK1 antagonists are effective as antidepressants (Rupniak and Kramer 1999), and results in NK1R–/– mice suggest they may act by downregulating 5-HT1A autoreceptors to restore 5-HT neuronal activity (Fig. 1). These results from different
gene knockout models implicate 5-HT1A receptors in anxiety behaviors. Similarly, the PET-1–/– mouse has an 80% loss of 5-HT immunostaining and also displays aggressive and anxiety behaviors (Hendricks and others 2003), indicating that selective loss of 5-HT-positive neurons can also lead to an anxiety phenotype (Fig. 2).

The rescue of the anxiety phenotype of 5-HT1A–/– mice was accomplished by genetic incorporation of a doxycycline-inducible CAMKII promoter transgene to direct expression to postsynaptic areas including the cortex, hippocampus, and amygdala (Gross and others 2002). Although expression from the CAMK promoter in these regions does not precisely match 5-HT1A RNA localization, the rescue suggests that expression of the 5-HT1A receptor at these postsynaptic regions, but not presynaptically, is sufficient to rescue the anxiety behavior. Importantly, induction of 5-HT1A receptor expression in the early postnatal “critical” period (postnatal days 5-21) was sufficient to reverse anxiety behavior to the wild-type level in these mice. Thus, early postnatal transcriptional regulation of the endogenous 5-HT1A receptor gene in the hippocampus or forebrain may play a role in later behavioral phenotypes (Fig. 2). In 5-HT1A–/– mice, impaired function of the dentate gyrus and reduced spatial memory are observed indicating hippocampal dysfunction (Sarnyai and others 2000). In addition, pharmacological block of the 5-HT1A receptor or of serotonin formation inhibits synaptogenesis of dentate granule cells (Yan and others 2000). In postnatal hippocampus birth, 5-HT1A receptor expression and protein levels are increased owing to glucocorticoid receptor (Gor and others 1997; Faber and Haring 1999). The critical period corresponds to a time of extensive neuronal remodeling, particularly in the hippocampus (McEwen 2001; Vreugdenhil and others 2001). Glucocorticoids mediate detrimental effects such as shrinkage and loss of hippocampal neurons, particularly during this period (Fig. 2). Elevation of glucocorticoids by early postnatal stress (e.g., maternal deprivation) can lead to lifelong exacerbation of stress responses in the adult (McEwen 1999; Liu and others 2000; Lee and McEwen 2001; Meaney 2001). The 5-HT1A receptor is a major regulator of the hypothalamic function of the hippocampus (Hanley and Van de Kar 2003) and is enriched in the hippocampus where it is subject to strong glucocorticoid repression (Mendelson and McEwen 1992; Zhao and Cinarrello 1995; Meijer and de Kloet 1998) via binding of glucocorticoid receptors to a novel negative glucocorticoid element (nGRE) (Ou and others 2001) or inhibition of NF-kB elements (Wissink and others 2000) (Fig. 4). Following postnatal maternal deprivation, hippocampal CA1 5-HT1A receptors are increased owing to glucocorticoid receptor desensitization (Vazquez and others 1996; Vazquez and others 2000; Weaver and others 2001), whereas in the adult, 5-HT1A RNA is decreased in the hippocampal dentate gyrus following chronic stress (Lopez and others 1999). These observations show that early postnatal hippocampal/forebrain 5-HT1A receptor regulation may differ from the adult and could determine anxiety-like behavior in the adult rodent. These results are consistent with findings that early life stress in humans could predispose to depression and that there is interaction between early life stress and the short allele of 5-HTT polymorphism to increase this predisposition (Caspi and others 2003). Similarly, reduction in hippocampal 5-HT1A receptor expression in early life may exacerbate the glucocorticoid response to stress, adversely affecting neurogenesis and maturation of hippocampal neurons (Malberg and Duman 2003) (Fig. 2).

5-HT1A Receptor and Antidepressant-Induced Neurogenesis

Since the initial finding that chronic antidepressant treatment induces neurogenesis in the hippocampal dentate gyrus (Malberg and others 2000), several studies have addressed the role neurogenesis could participate in in the behavioral action of antidepressants (Benninghoff and others 2002; Duman 2004). Although stress tends to reduce hippocampal expression of neurotrophins such as brain-derived neurotrophic factor (BDNF), antidepressants, electroconvulsive therapy, and exercise tend to upregulate BDNF or VEGF and are associated with increase in neurogenesis or antidepressant behavioral response (Conti and others 2002; Fabel and others 2003; Altar and others 2004; Duman 2004). In BDNF+/- (reduced BDNF expression) or dominant-negative TRKB-expressing mice (reduced BDNF signaling), antidepressants (fluoxetine, imipramine) failed to enhance performance in the forced swim test, a measure of depressed behavior (Saarelaenen and others 2003). Interestingly, BDNF is also implicated in raphe differentiation and serotonergic development in vivo (Galter and Unsicker 2000; Rumajogee and others 2002; Hensler and others 2003), which appears to be negatively regulated by 5-HT1A receptors (Rumajogee and others 2004).

Recently, the 5-HT1A receptor has been implicated in antidepressant-induced enhancement of neurogenesis and behavioral improvement (Santarelli and others 2003). In 5-HT1A–/– mice, chronic TCA treatment induced neurogenesis and improvement in the novelty suppressed feeding test but SSRI treatment was without effect. Similarly, the effect of 5-HT1A agonists to enhance hippocampal neurogenesis and reduce novelty suppression responses was blocked in 5-HT1A–/– mice. It remains unclear how inhibitory 5-HT1A receptors (Fig. 1) stimulate neurogenesis. However, in the hippocampus the 5-HT1A receptor is expressed in astroglia as well as neurons, where it stimulates release of pro-survival factors (Wilson and others 1998; Azmitia 2001), perhaps by coupling to stimulatory pathways such as calcium mobilization and MAPK activation that are observed in nonneuronal cells (Raymond and others 1999). Interestingly, anxiolytic 5-HT1A partial agonists (buspirone, flesinoxan) but not full agonists or neutral antagonists display inverse agonist activity for 5-HT1A activation of AC type II (Albert and others 1999), a pathway observed in the hippocampus that could mediate CREB activation and neurogenesis. These results indicate a critical role for the 5-HT1A receptor in hippocampal neurogenesis induced by SSRI antidepressants that target the 5-HT system, but additional mechanisms...
are recruited by TCAs that target multiple systems. Use of x-ray irradiation to oblate proliferative cells in the hippocampus blocked both neurogenesis and the behavioral improvements induced by antidepressants (Santarelli and others 2003). This suggests a role for neurogenesis in the antidepressant response, but irradiation may exert additional damage that could block behavioral responses. However, there was no clear effect of irradiation on behavior. Thus, although neurogenesis may play a role in antidepressant action in the adult, it does not appear to mediate altered behavior in the adult. As discussed above, early postnatal alterations may have a much greater role in establishing long-term adult behavior.

In contrast to animal models, in depressed human subjects, the major changes observed by imaging studies in vivo or neuroanatomical studies of postmortem tissue occur in cortical regions such as the dorsolateral prefrontal cortex and anterior cingulate cortex as described above (Mayberg 2003; Rajkowska 2003). Furthermore, memory processing involving communication between the hippocampus and anterior cingulate cortex is impaired in depression (Bremner and others 2004). The reduced 5-HT neurotransmission coupled with early life stress events that elevate glucocorticoids (red arrows) could lead to altered hippocampal development and circuitry, resulting in reduced hippocampal, amygdala, and cortical volumes that progress with age. A key stressful event (large red arrow) could trigger the first episode of depression. Treatment with SSRI has the best effect in the first episode in the favorable genotype; if a second depression episode ensues, progressive deterioration makes SSRI treatment less effective (dose increases), leading to increased likelihood of recurring depression episodes and suicide attempts.

Fig. 11. Interaction between 5-HT1A autoreceptors, genotype and environmental stress, and depression and recovery. Shown is the influence of genotype, 5-HT1A autoreceptor, life stress events, and SSRI treatment on the development and course of depression over the lifetime of two hypothetical individuals. The upper individual has a “nonpredisposing” genotype, and the level of 5-HT1A autoreceptors is low (light blue arrows); the lower individual has a “predisposing” genotype with higher levels of 5-HT1A autoreceptors, and lowered 5-HT neurotransmission. The reduced 5-HT neurotransmission coupled with early life stress events that elevate glucocorticoids could lead to altered hippocampal development and circuitry, resulting in reduced hippocampal, amygdala, and cortical volumes that progress with age. A key stressful event could trigger the first episode of depression. Treatment with SSRI has the best effect in the first episode in the favorable genotype; if a second depression episode ensues, progressive deterioration makes SSRI treatment less effective (dose increases), leading to increased likelihood of recurring depression episodes and suicide attempts.

New insights into the functional role of specific genetic changes in predisposition to endophenotypes associated with mental illness.

5-HT1A Receptor Gene Repression in Depression: Guilty by Association?

In summary, several findings indicate a key role for 5-HT1A receptors in the etiology and treatment of disorders that involve the serotonin system including major depression, anxiety, and suicide. As discussed above, findings from animal models and human imaging and postmortem studies appear to converge on the serotonin system as an important potential initiator of depression and mediator of antidepressant actions (Fig. 11). The critical role of the 5-HT1A receptor in regulation of serotonergic raphe activity via presynaptic autoreceptors and its importance in mediating many of the postsynaptic actions of 5-HT1A in limbic, cortical, hypothalamic, and other brain regions make the regulation of this receptor important to mental illness. Increased levels of 5-HT1A autoreceptor, or decreased 5-HT neuronal number mediated in part by autoreceptors, tend to reduce 5-HT neurotransmission. Reduced levels of activity of postsynaptic 5-HT1A receptors is implicated in long-term regulation of gene expression, neurogenesis especially in the hippocampus, and establishment of behavioral phenotypes such as anxiety or depression.
Importantly, the stress axis can also downregulate hippocampal 5-HT1A receptors and decrease hippocampal neurogenesis and differentiation. The same dramatic impairments of hippocampal structure as observed for stress or glucocorticoid treatment have not been reported for 5-HT1A+/− or PET-1+/− (with 80% loss of 5-HT expression [Hendricks and others 2003]), suggesting that decreased 5-HT1A signaling may potentiate the effects of stress, leading to hippocampal dysfunction and ultimately to aberrant cortico-limbic communication. Ultimately, in man it is likely to be cortical alterations that produce the symptoms of major depression that are not easily modeled in rodents.

Studies associating the 5-HTTLPR functional promoter polymorphism with personality traits and indices of mental illness, and our evidence for a role of the C(−1019)G polymorphism in the transcriptional regulation of the 5-HT1A receptor gene and its association with depression and completed suicide, further suggest a role for reduced activity of the 5-HT system in predisposition to mood disorders and suicide. A significant advance is the demonstration that the C(−1019)G 5-HT1A polymorphism blocks NUDR function. Thus, a single nucleotide alteration of a specific DNA regulatory element can block protein-DNA interactions leading to transcriptional changes that may have a subtle effect on the overall levels of receptor but are correlated with depression (Fig. 10). These and ongoing association studies suggest the importance of the candidate gene approach as a valid way to identify functionally relevant markers for mental illness. Identification of gene regulatory and polymorphisms in candidate genes associated with depression may permit a more precise categorization of depression, with different latency, severity, drug treatment outcomes, and associated comorbidity, such as suicide, anxiety, and so on. For example, the short allele of the 5-HTTLPR polymorphism is associated with weak response to SSRI, but pindolol augmentation was effective (Zanardi and others 2001). The major weakness of this approach is the strength of association and variation of allele frequency with ethnicity (Stephens and others 2001). With a sufficient selection of characterized polymorphisms, associations with mental illness should be feasible despite variations in ethnicity.

Taken together, data from animal models, human imaging, and postmortem and genetic association studies argue that the reduced 5-HT neurotransmission due to altered transcriptional regulation of the 5-HT1A receptor is associated with a predisposition to depression. We propose the verdict of guilty as charged.

References


