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Focus on
The 5-HT1A receptor: emerging role of a gene regulatory variant in psychopathology and pharmacogenetics

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While multiple lines of evidence implicate the 5-HT1A receptor in the pathophysiology of anxiety and depression as well as in the mechanism of action of anxiolytics/antidepressants, its relevance to the therapeutic effectiveness of these drugs has been a matter of considerable debate (for review see Griebel, 1995; Hensler, 2003; Hjorth et al., 2000; Lesch et al., 2003). In the current issue of the *International Journal of Neuropsychopharmacology*, however, both Serretti et al. (2004) and Lemonde et al. (2004) make a strong argument for contribution of a functional 5-HT1A receptor gene variant in the pharmacogenetics of antidepressant treatment with prototypic tricyclics and selective serotonin reuptake inhibitors (SSRIs). Furthermore, the third study in this series by Huang and associates (2004) reveals an association of allelic variation of 5-HT1A receptor expression in a wide spectrum of psychopathology including schizophrenia, substance abuse, and panic disorder. Not unexpectedly, the failure to detect a consistent effect of this gene variation on 5-HT1A receptor functionality in the mature brain as indicated by both receptor binding in post-mortem brain and in-vivo receptor responsivity further supports a critical role of the 5-HT1A receptor in engineering neurodevelopmental processes which may have the potential to set the stage for the brain's permissiveness for psychopathology in later life. The availability of an increasing number of functional gene variants within the serotonergic pathway together with integration of emerging concepts of developmental genetics of complex traits will provide the groundwork for the molecular dissection of syndromal dimensions and treatment response.

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See Huang et al. (this issue). Human 5-HT1A receptor C(–1019)G polymorphism and psychopathology; Lemonde et al. (this issue). Association of the C(–1019)G 5-HT1A functional promoter polymorphism with antidepressant response; Serretti et al. (this issue). The C(–1019)G polymorphism of the 5-HT1A gene promoter and antidepressant response in mood disorders: preliminary findings.

Allelic variation of 5-HT1A receptor expression and psychopathology

The 5-HT1A receptor is encoded by an intronless gene (*HTR1A*) located on human chromosome 5q12.3. Several rare missense polymorphisms, including the Gly22Ser variant which results in altered agonist-elicited down-regulation, have been found within the protein coding of *HTR1A*. Moreover, Lemonde and co-workers (2003) reported a functional C(–1019)G single nucleotide polymorphism (SNP) in the transcriptional control region of *HTR1A* (HTR1A-1019) and demonstrated in in-vitro experiments that the G variant displays differential binding efficiency of the repressors/enhancer-type transcriptional regulator NUDR/DEAF-1. NUDR/DEAF-1 is co-expressed with both pre- and post-synaptic 5-HT1A receptors, but its regulation of *HTR1A* transcription may differ in presynaptic raphe vs. post-synaptic target cells (Lemonde et al., 2003).

Although initial association studies of the *HTR1A* variations produced ambiguous results in affective disorders (Arias et al., 2002; Nishiguchi et al., 2002), Lemonde and co-workers (2003) also showed that the G variant of the HTR1A-1019 polymorphism is associated with severe depression and suicidality. Taking the considerable comorbidity of depression and anxiety disorders into account it came as no surprise

that associations of the G variant with anxiety- and depression-related personality traits, particularly with higher scores in Neuroticism and Harm Avoidance, as well as with the agoraphobic subtype of panic disorder were also reported (Rothe et al., 2004; Strobel et al., 2003). These findings have now been further extended by Huang et al. (2004) who report an association of the HTR1A-1019 polymorphism with panic disorder as well as in schizophrenia and substance use disorder.

Early drug-challenge studies had revealed an attenuation of 5-HT1A receptor-induced hypothermic and neuroendocrine responses in patients with panic disorder and depression, reflecting dysfunction of both pre- and post-synaptic 5-HT1A receptors (Lesch et al., 1990b, 1992). Likewise, a decrease in ligand binding to 5-HT1A receptors as assessed by positron emission tomography (PET) has been shown in forebrain areas and in the raphe complex of affective and panic disorder patients (Drevets et al., 1999; Sargent et al., 2000). Down-regulation and hyporesponsivity of 5-HT1A receptors in patients with major depression do not seem to be reversed by antidepressant drug treatment (Lerer et al., 1999; Lesch et al., 1990a, 1991; Sargent et al., 2000), raising the possibility that low pre- and post-synaptic 5-HT1A receptor function is a trait feature and therefore a pathogenetic mechanism of disease. Taken together, the findings derived from pharmacological, imaging, and genetic approaches consistently implicate dysfunctional 5-HT1A receptors in the pathophysiology of anxiety disorders and syndromal dimensions of depression, psychosis, and substance abuse.

5-HT1A receptor gene variants and antidepressant treatment response

As the detailed mechanism of antidepressant responses continues to be enigmatic, studies have shifted focus from adaptive changes in neurotransmitter release, uptake, and metabolism to modulation of gene expression, synaptic plasticity, neurogenesis, and neuronal survival (Lesch, 2001; Santarelli et al., 2003). Treatment response to serotonergic antidepressant and anxiolytic drugs, such as the prototypical tricyclic clomipramine, and the SSRIs, such as fluvoxamine, paroxetine, citalopram, and sertraline, is influenced by genetic factors and depends on the structure or functional expression of various gene products that mediate serotonergic signalling. While treatment response is believed to involve both genetic and environmental factors, the contribution of an individual gene to drug response is likely to be modest. However, interactions between different genes may result in a dramatic modification of drug response (additive, non-additive or multiplicative gene effects). The challenge faced by research into the genetic basis of drug response is to identify genes of relatively small effect against a background of substantial genetic and environmental variation.

The effects of 5-HT1A receptor selective agents, such as the agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and the partial agonists ipsapirone (IPS) and gepirone, have been extensively studied in rodents (De Vry, 1995). Both agonists and partial agonists induce a dose-dependent anxiolytic effect, which correlates with the inhibition of serotonergic neuron firing, decrease of 5-HT release as well as the reduction of 5-HT signalling at post-synaptic target receptors. Blockade of the negative feedback by the selective 5-HT1A receptor antagonist WAY 100635 increases firing of the serotonergic neurons but exerts no effect on 5-HT neurotransmission or behaviour (Olivier and Miczek, 1999), while the combination with SSRIs augments increases in 5-HT levels in terminal regions. Since a given genetic predisposition, such as allelic variation in 5-HT1A function increases susceptibility to anxious or depressive features as well as depression and panic disorder, it may also lead to less favourable antidepressant responses in patients affected by mood disorders. Preliminary evidence that allelic variation of 5-HT1A receptor expression influences the response to antidepressant treatment is now provided by two independent studies. Serretti and colleagues (2004) assessed the severity of depressive symptoms in 151 patients with major depression and 111 bipolar patients before and following 6 weeks of treatment with the SSRI fluvoxamine and demonstrate that in bipolar disorder but not in unipolar depression, patients homozygous for the C variant of the HTR1A-1019 polymorphism showed a better response compared to carriers of the G allele. Interestingly, the results failed to reveal an interaction between the HTR1A-1019 polymorphism and a previously reported effect of a functional gene variant of the 5-HT transporter.

Lemonde et al. (2004) also report that antidepressant response to the SSRI fluoxetine, noradrenaline reuptake inhibitor nefadozone, and 5-HT1A agonist flibanserin, which desensitize the 5-HT1A autoreceptor as one of their mechanisms of action, was associated with HTR1A-1019 polymorphism in 118 depressed patients. Patients homozygous for the G variant of the HTR1A-1019 polymorphism improved significantly less on flibanserin and in pooled antidepressant treatment groups were twice as likely

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to be non-responders as those with the C/C genotype. These findings further corroborate the hypothesis that genetic variations in *HTR1A* may not only predispose to psychiatric disorders, but may also contribute to individual differences in responsiveness to antidepressant treatment.

5-HT1A receptors in the neurodevelopmental perspective

Intriguingly, Huang and associates (2004) have also been able to demonstrate that 5-HT1A receptor binding in the prefrontal cortex of suicide victims was not associated with genotype. These findings suggest that 5-HT1A receptor availability in the mature brain is modulated by factors that obscure the effects of gene regulatory mechanisms on its expression. Furthermore, it remains unclear whether allelic variation of 5-HT1A receptor function is equally operative at both the somatodendritic autoreceptor and the post-synaptic receptor level. Somatodendritic 5-HT1A autoreceptors are predominantly located on 5-HT neurons and dendrites in the brainstem raphe complex. Their activation by 5-HT or 5-HT1A agonists decreases the firing rate of serotonergic neurons and subsequently reduces the synthesis, turnover, and release of 5-HT from nerve terminals in projection areas. Post-synaptic 5-HT1A receptors are widely distributed in forebrain regions that receive serotonergic input, notably in the cortex, hippocampus, septum, amygdala, and hypothalamus. Their activation results in membrane hyperpolarization and decreased neuronal excitability. While 5-HT1A receptor expression is also modulated gender-dependently by steroid hormones, 5-HT1A receptor-mediated signalling is, in turn, an important regulator of downstream gene expression through its coupling to G proteins that inhibit adenylyl cyclase and modulation of GIRK2 channels.

In order to test the effect of HTR1A-1019 genotype on 5-HT1A receptor responsivity in vivo, we examined hypothermic and neuroendocrine responses to the selective 5-HT1A receptor ligand IPS in 27 healthy subjects who had received 0.3 mg/kg of IPS or placebo under double-blind, random-assignment conditions. 5-HT1A receptor-mediated thermoregulatory ($F_{2,24}=0.06$, $p=0.93$) and ACTH/cortisol responses ($F_{2,24}=0.67$, $p=0.52$ and $F_{2,24}=0.00$, $p=0.99$ respectively) to IPS revealed no significant difference between genotypes and pre- or post-synaptic 5-HT1A function (Lesch et al., 2004) (Figure 1). Despite the limitations of the sample size, these preliminary results provide further support for the notion that 5-HT1A receptor responsivity in the adult brain is not robustly influenced by the HTR1A-1019 polymorphism.

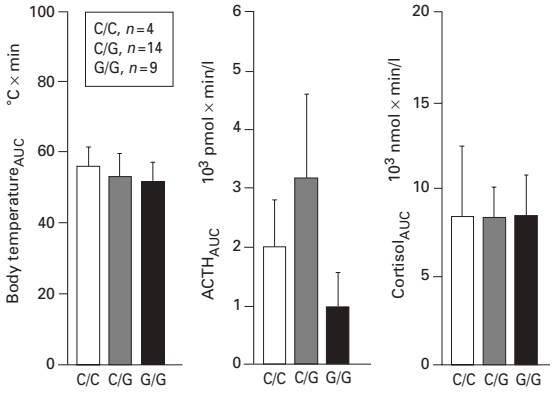

Figure 1. Effect of HTR1A-1019 genotype on pre- and post-synaptic 5-HT1A receptor responsivity in vivo. Hypothermic and neuroendocrine responses to the selective 5-HT1A receptor ligand ipsapirone (IPS) were examined in 27 healthy subjects. IPS tests were conducted at rest in bed and the subjects who were familiar with the investigative setting remained awake throughout the study. Each subject received 0.3 mg/kg IPS hydrochloride or identical placebo tablets orally at 16:00 hours under double-blind, random-assignment conditions on separate days as previously reported (Lesch et al., 1991). For measurement of plasma ACTH and cortisol, blood was collected at −30, 0, 15, 30, 45, 60, 75, 90, 105, 120, 150 and 180 min and sublingual body temperature was recorded at −60, −30, 0, 30, 60, 90, 120, 150, and 180 min using a high resolution thermistor probe. The hypothermic and ACTH/cortisol responses to IPS were calculated as the net (IPS–placebo difference) area under the curve ($AUC_{0\text{-}180}$) using trapezoidal integration. HTR1A-1019 genotypes were determined as reported by Strobel and co-workers (2003). The effect of the HTR1A-1019 genotype on IPS-induced hypothermia and ACTH/cortisol concentrations was tested by analysis of variance (ANOVA). 5-HT1A receptor-mediated thermoregulatory and neuroendocrine responses to IPS revealed no significant difference between HTR1A-1019 genotypes and pre- or postsynaptic 5-HT1A function.

Converging lines of evidence that 5-HT1A receptor deficiency or dysfunction is involved in anxiety and mood disorders encouraged investigators to genetically manipulate the 5-HT1A receptor in mice. As anticipated, mice with a targeted inactivation of the *HTR1A* display a spontaneous phenotype that is associated with a gender-modulated and gene/dose-dependent increase of anxiety-related behaviour and stress reactivity in several conflict paradigms (Lesch et al., 2003; Toth, 2003). Activation of pre-synaptic 5-HT1A receptors provides the brain with an auto-inhibitory feedback system controlling 5-HT neuro-

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transmission. Thus, enhanced anxiety-related behaviour probably represents a consequence of increased terminal 5-HT availability resulting from the lack or reduction in pre-synaptic somatodendritic 5-HT1A autoreceptor negative feedback function (Lesch and Mössner, 1999).

This mechanism is also consistent with recent theoretical models of fear and anxiety that are primarily based upon pharmacologically derived data. The cumulative reduction in serotonergic impulse flow to septo-hippocampal and other limbic and cortical areas involved in the control of anxiety is believed to explain the anxiolytic effects of ligands with selective affinity for the 5-HT1A receptor in some animal models of anxiety-related behavior. This notion is based, in part, on evidence that 5-HT1A agonists (e.g. 8-OH-DPAT) and antagonists (e.g. WAY 100635) have anxiolytic or anxiogenic effects respectively. However, to complicate matters further, 8-OH-DPAT has anxiolytic effects when injected in the raphe nucleus, whereas it is anxiogenic when applied to the hippocampus. Thus, stimulation of post-synaptic 5-HT1A receptors has been proposed to elicit anxiogenic effects, while activation of 5-HT1A autoreceptors is thought to induce anxiolytic effects via suppression of serotonergic neuronal firing resulting in attenuated 5-HT release in limbic terminal fields.

Since the 5-HT1A receptor is expressed differentially in distinct brain subsystems, it was of interest to clarify whether pre- or post-synaptic receptors are required to maintain normal expression of anxiety-related behaviour in both humans and the animal model. With an elegant conditional rescue approach, Gross and coworkers (2002) showed that expression of the 5-HT1A receptor in the hippocampus and cortex but not in the raphe nuclei is required to rescue the behavioural phenotype of 5-HT1A knockout mice. The findings indicate that deletion of the 5-HT1A receptor in mice, specifically in forebrain structures, results in a robust anxiety-related phenotype and that this phenotype in 5-HT1A knockout mice is caused by the absence of the receptor during a critical period of postnatal development, whereas inactivation of 5-HT1A in adulthood does not affect anxiety. Even more importantly, the findings further substantiate the view of a central role for 5-HT and the 5-HT1A receptor in the early development of neurocircuits mediating emotion (Lesch, 2003). Although there is converging evidence that the 5-HT1A receptor mediates depression- and anxiety-related behaviour, the neurodevelopmental mechanism that renders 5-HT1A receptor-deficient mice more anxious is highly complex and remains to be elucidated in its details (Gross and Hen, 2004).

In conclusion, allelic variation in 5-HT1A receptor expression seems to play a critical role in the development and modulation of individual differences in anxiety- and depression-related personality traits as well as in the pathophysiology of anxiety disorders and syndromal dimensions of depression, psychosis, and substance abuse. Evidence that this polymorphism also influences therapeutic responses to serotonergic agents may have implications for tailoring individual antidepressant/anxiolytic treatment.

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Statement of Interest

None.

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