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GUEST EDITORIAL

Hallucinations: psychopathology meets functional genomics

Hallucinations in major psychosis including schizophrenic disorders are characterized by recurrent, intrusive, and enervating involuntary perceptions in the absence of external stimuli. Hearing voices is the most common form of hallucination, and derogatory or threatening messages are particularly common. Considerable progress has been made in the elucidation of the neuropsychological processes accompanying auditory as well as visual hallucinations.[1] Assessment of the functional neuroanatomy of hallucinations in schizophrenic disorders using neuroimaging strategies such as positron emission tomography (PET) has implicated multiple brain regions including the prefrontal cortex and auditory-linguistic association cortices as well as limbic/paralimbic, striatal, and thalamic systems.[2] In the neurobiological dimension it is becoming increasingly evident that altered synaptic plasticity involving dopaminergic, glutamatergic, GABAergic, and serotonergic neurotransmitter systems in conjunction with predisposing genes contribute to the generation and modulation of hallucinations. Finally, molecular strategies are gaining momentum for the validation of the concept of interindividual differences in the susceptibility to distinct clinical forms of hallucinations. These approaches address the pertinent question: Is there a genetic basis for the neural correlates of hallucinations?

Functional genomics of the 5-HT transporter

On pages 328–332 of this issue, Malhotra and coworkers report an association between hallucinations in neuroleptic-free patients with schizophrenic disorders and homozygosity for the long variant of a repetitive element in the 5′-regulatory region of the serotonin (5-HT) transporter gene (SLC6A4). The findings indicate that hallucinations may be generated or modulated by specific hypersensitive 5-HT subsystems that are preferentially kindled by hallucinogenic input and that assessment of genetic factors may allow dissection of the complex clinical presentation of schizophrenia from vulnerability to this disease. This repetitive element, the 5-HT transporter (5-HTT)-linked polymorphic region (5-HTTLPR), confers allele-dependent differential transcriptional activity on the 5-HTT promoter.[3] Studies on the effect of different 5-HTTLPR genotypes on functional 5-HTT expression demonstrated that lymphoblastoid cells homozygous for the long (*l*) variant of the 5-HTTLPR produced higher concentrations of 5-HTT mRNA than did cells containing one or two copies of the short (*s*) form.[4] Membrane preparations from *l*/*l* lymphoblasts showed higher inhibitor binding than did *s*/*s* cells and 5-HT uptake was higher in cells homozygous for the *l* form of the 5-HTTLPR than in cells carrying one or two endogenous copies of the *s* variant of the promoter. In postmortem brain, 5-HTT mRNA concentrations were significantly lower in the brainstem raphe complex of individuals with *l*/*s* and *s*/*s* as compared to *l*/*l*, and a similar though less pronounced genotype effect was found for 5-HTT inhibitor binding in brain stem and striatum.[5] It has previously been suggested that the *s* variant and thus low 5-HTT expression is associated with anxiety- and depression-related personality traits and may influence the risk of developing affective spectrum disorders.[4,6]

5-HT transporter-mediated fine-tuning of 5-HT neurotransmission

In psychotic patients with two *l* variants of the 5-HTTLPR genotype, the increased frequency and intensity of hallucinations are therefore likely to be associated with the functional consequences of higher than average 5-HTT availability. What are the likely consequences? The regional variation of 5-HTT expression and the complex autoregulatory processes of 5-HT function which are operational in different brain areas are leading to a plausible hypothesis for a role of 5-HT uptake function in the generation and modulation of hallucinations. While 5-HT acts like a master control neurotransmitter within this highly complex system of neural communication mediated by multiple pre- and postsynaptic 5-HT receptor subtypes, 5-HT uptake into the presynaptic neuron by a single protein represents a functional 'bottle neck'. Thus, the 5-HTT is a major regulator of extracellular 5-HT concentrations, and enhanced ability of the 5-HTT for a rapid 5-HT clearance following release elicits an acute decrease of 5-HT both in the synaptic cleft and in the vicinity of serotonergic cell bodies and dendrites in the raphe complex (Figure 1). Postsynaptic 5-HT receptors, particularly of the 2A, 2C, and 1A subtype (the subtypes that have also been implicated in the effect of hallucinogenic compounds like LSD on glutamatergic and many other neurons) respond to low intrasynaptic 5-HT levels with an increase in responsivity possibly involving enhanced sensitivity at the level of the receptor and/or its signal transduction pathway. Further-

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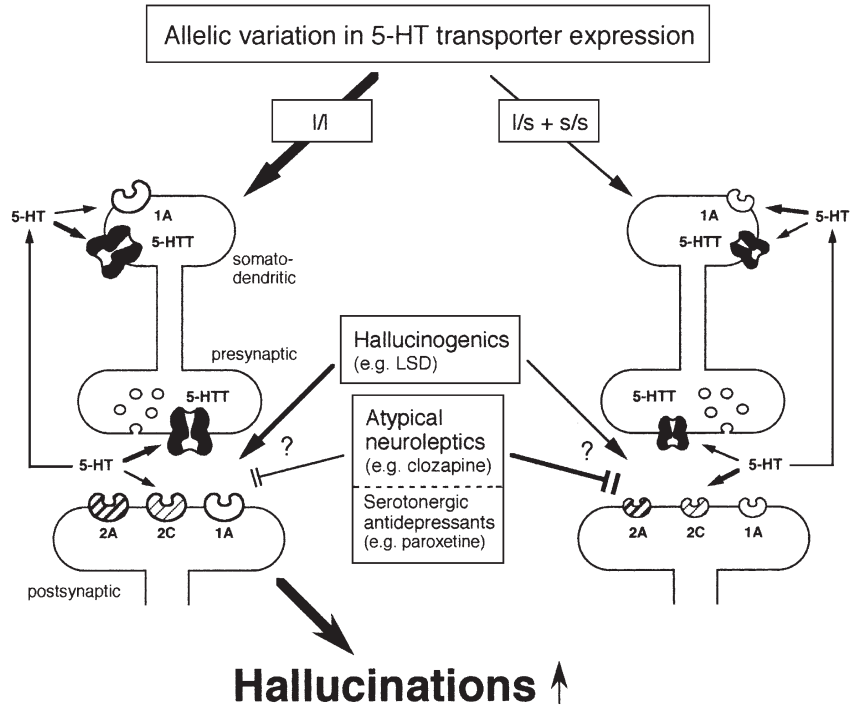

Figure 1 Allelic variation of 5-HT transporter (5-HTT) expression as a determinant of adaptive autoregulation of 5-HT transmission and its response to the effects of hallucinogenics, atypical neuroleptics, and long-term treatment with selective 5-HT reuptake inhibitors. The susceptibility to hallucinations in psychotic patients with two alleles of the long 5-HTTLPR variant (*l*/*l*) may be a consequence of regional variation of 5-HT receptor subtype and 5-HTT distribution that underly complex autoregulatory processes operational in different brain areas. The genetically-driven enhanced ability of high 5-HTT function for a rapid 5-HT clearance following release into the synaptic cleft forces prompt removal of 5-HT in the vicinity of serotonergic terminals, thus leading to an increased sensitivity of postsynaptic 5-HT receptors. In addition, removal of 5-HT near serotonergic cell bodies and dendrites in the raphe complex exerts a somatodendritic 5-HT_{1A} receptor-mediated disinhibition that may cause a net increase in 5-HT release in these individuals. Complex adaptive mechanisms are also likely to play a role in the antihallucinatory effects of atypical neuroleptic and selective 5-HT reuptake inhibitors.

more, partial failure of low extracellular 5-HT to maintain the somatodendritic 5-HT1A receptor-mediated negative feedback may lead to an overall increase of 5-HT release in individuals or patients with long 5-HTTLPR alleles. In the view of a highly dynamic serotonergic system it is therefore conceivable that variations in the 5-HT uptake cause the serotonergic function to equilibrate at distinct setpoints. It would be of considerable interest, if future studies could clarify whether individuals with an *l*/*l* 5-HTTLPR genotype would be more prone to the psychotomimetic effects of hallucinogenics, and whether acute treatment with atypical neuroleptics, such as clozapine, olanzapine, risperidone was more effective in ameliorating hallucinatory symptomatology in psychotic patients with this genotype (Figure 1).

Previous postmortem and neuroimaging studies of 5-HT receptor binding in schizophrenic patients, however, did not consistently report changes as predicted by the hypothesis of increased receptor sensitivity due to high 5-HTT availability. Patients with schizophrenia showed reduced radioligand binding to 5-HT reuptake sites in distinct regions of the brain,[7,8] whereas increases of 'atopic' 5-HTT mRNA have been reported in the frontal and temporal cortex, possibly indicating reactivation of 5-HTT expression that has been repressed after completion of brain development.[9,10] Finally, among the various 5-HT receptors, no consistent association with schizophrenia has as yet been detectable at the molecular level, and the reported association of schizophrenia to a silent polymorphism within the coding region of the 5-HT2A receptor gene requires replication in additional family-based association studies as well as identification of a functional mutation in the gene's regulatory region that should be in linkage disequilibrium with this variant.[11]

5-HT transporter and brain 5-HT homeostasis

Progress in transgenic and gene transfer technologies with focus on the 5-HTT are currently changing our understanding of the relevance of adaptive 5-HT uptake function in brain development and plasticity as well as processes underlying neurodegeneration. It is therefore not particularly difficult to reconcile a dysfunction of serotonergic signaling, possibly caused by the 5-HTT and mediated via various 5-HT receptors with the current concept of schizophenia as a disorder of neurodevelopment. However, despite evidence for a critical role of the 5-HTT in the integration of synaptic connections in the mammalian brain during development, adult life, and old age, detailed knowledge of the

molecular mechanisms involved in these processes is just beginning to emerge. Early expression of 5-HT in developing midbrain raphe neurons and their projecting terminals prior to synaptogenesis and onset of serotonergic signaling, indicates that it is an important regulator of morphogenetic activities during early embryonic development, including cell proliferation, migration and differentiation.[12,13] These phylogenetically ancient functions are reiterated in the developing mammalian brain. An increasing body of evidence suggests that the 5-HTT plays a critical role in the fine-tuning of brain morphogenesis. While in adult life 5-HTT expression appears to be restricted to raphe neurons, it has been detected in several other regions including cingulate, entorhinal, and frontopolar cortex, as well as hippocampus (CA1-3, dentate gyrus), septum, and endopyriform nucleus during pre- and postnatal development.[10] Dense transient serotonergic innervation of the somatosensory, visual, and auditory cortices originates in the thalamus rather than in the midbrain raphe complex. 5-HT is detected in thalamocortical fibers, and cortical labeling of 5-HT disappears after thalamic lesions. While thalamic glutamatergic neurons do not synthesize 5-HT, they take up exogenous 5-HT through transiently expressed 5-HTT located on thalamocortical axons and terminals. Internalized 5-HT may be stored and used for serotonergic signaling or could exert an intraneuronal control on thalamic maturation.[14,15] The pivotal role of the 5-HTT in the maintenance of brain 5-HT homeostasis during development and later life is further supported by studies in mice with a targeted inactivation of the 5-HTT.[16]

Etiologic heterogeneity of schizophrenic disorders

Apart from the modest but steady progress in the elucidation of complex genetic influences contributing to the pathogenic processes in various psychiatric disorders, prematurely raised expectations regarding the identification of major genes linked to familial forms of schizophrenia have led to a great deal of disappointment. However, there is now an increasing body of evidence that periodic catatonia is a subtype of familial schizophrenia, with evidence for an autosomal dominant mode of inheritance and anticipation in which a moderate gene effect may be operative and thus amenable to positional cloning.[17] Although several distinct subtypes of schizophrenia may share factors which determine hallucinatory symptoms, genetic heterogeneity and a substantial but varying environmental component complicates identification of predisposing genes. Moreover, as in other genetically complex disorders, a susceptibility gene, or a gene like the 5-HTT that modifies the clinical phenotype, alone is neither necessary nor sufficient to cause the disease. While only few structural changes in the brain are directly related to schizophrenic disorders, the failure to adapt to external challenges appears to be highly relevant to its pathogenesis. The genetic component in the etiology of schizophrenic disorders is therefore probably more related to dysregulation of gene expression with subsequent alterations in synaptic plasticity and adaptation, than to the generation of gene products with structural changes.

Let's wake up and smell the coffee!

In agreement with these views, schizophrenia is now generally thought to be an etiologically and clinically heterogeneous syndrome caused by complex interaction of both genetic and environmental factors. Allelic variation in functional 5-HTT expression may play a crucial role in synaptic plasticity, thus setting the stage for expression of complex traits and their associated behavior throughout adult life. On the other hand, there is a growing body of evidence that schizophrenia is a neurodevelopmental disorder with altered cortical cytoarchitecture and excessive synaptic pruning resulting in a complex pathophysiology.[18,19] Therefore, the differentiation of psychopathological distinct subtypes is of particular importance for the dissection of the complex genetics of schizophrenic disorders.[20] While in most psychiatric disorders identification of major disease genes is highly unlikely and pinpointing moderately effective susceptibility genes will probably continue to be difficult, more genes that modify of a specific clinical phenotype are likely be identified in the near future.

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