Furthermore, rescue experiments in cascade-disrupted mice show that the level of serotonergic function is sensitive to the level of expression of the transcriptional program that gives rise to 5-HT neurons (Lerch-Haner *et al*, 2008).

The irreversible alterations in brain serotonergic transcription are not lethal and therefore cascade-targeted mice provide a new way to investigate the impact of altered serotonergic function on animal behaviors and physiological processes that are relevant to many psychiatric and neurological disorders. Indeed, disruption of the serotonergic transcriptional cascade causes alterations in emotional behaviors (Hendricks *et al*, 2003). In addition, these approaches have provided experimental support, *in vivo*, for the hypothesis that abnormal serotonergic development contributes to SIDS vulnerability (Erickson *et al*, 2007; Hodges *et al*, 2008). They have also revealed maternal nurturing as a previously unrecognized 5-HT system-modulated behavior (Lerch-Haner *et al*, 2008). The accompanying high mortality rate of offspring born to cascade-targeted mothers forces a reassessment of the long-held view that the brain 5-HT system is not essential for physiological processes and animal survival.

The new genetic approaches created to study 5-HT neuron development and function support the idea that altered transcriptional programming of serotonergic signaling is a potential mechanism underlying behavioral and physiological pathogenesis. Future studies might be focused on determining the vulnerability of cascade activity to fetal and early postnatal exposure to environmental insults such as drugs and harmful stress. In addition, the identification of genetic variation that impacts cascade factor activity may reveal additional 5-HT-related risk factors for pathogenesis beyond the usual suspects.

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DISCLOSURE

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An Emerging Role for TARPs in Neuropsychiatric Disorders

The discovery of glutamate as the principal excitatory neurotransmitter in brain was followed by the identification and molecular cloning of the ionotropic glutamate receptor family, which comprises NMDA, AMPA, and kainate receptors. The AMPA receptor subfamily mediates fast synaptic neurotransmission important to diverse sensory, behavioral, and cognitive processes, including learning and memory. However, excessive AMPA receptor activity and subsequent excitotoxicity underlie central nervous system disorders ranging from stroke to epilepsy. It was hypothesized that the development of AMPA receptor antagonists to dampen aberrant neurotransmission would provide treatments for neurological illnesses. However, clinical trials have shown side effects for these antagonists and suggested a need for greater selectivity.

A seminal finding in AMPA receptor biology and neurotransmission was the discovery of stargazin, the protein mutated in stargazer mice, which show absence epilepsy and cerebellar ataxia. Cell biological and physiological studies showed that stargazin is an AMPA receptor auxiliary subunit and controls receptor trafficking, gating, and pharmacology. Subsequent studies have identified a family of related transmembrane AMPA receptor regulator proteins (TARPs). TARPs comprise γ-2 (stargazin), -3, -4, -5, -7, and -8 subunits, which are discretely distributed in specific neuronal and glial populations throughout the brain. Studies involving γ-8 knockout mice, which exhibit deficiencies in hippocampal neurotransmission, underscore the importance of TARPs both in region-specific control of AMPA receptor signaling, and in neurological disease—hippocampal excitotoxicity elicited by the AMPA receptor partial agonist, kainate, is abrogated in γ-8 knockout mice (Tomita *et al*, 2007).

Neuropsychiatric conditions such as schizophrenia, depression, and bipolar disorder are severe, multifactorial brain illnesses of mood, cognition, and behavior whose etiologies remain uncertain. Molecular analyses have found abnormal expression for key components of glutamatergic neurotransmission, including TARPs. Increased and decreased stargazin mRNA expression has been documented in post-mortem schizophrenic and major depressive disorder brains, respectively (Beneyto and Meador-Woodruff, 2006). Silberberg *et al* (2008) found certain *CACNG2* (the gene that encodes stargazin) allelic polymorphisms are associated with improved response to lithium, the classical treatment for bipolar disorder. Furthermore, chronic treatment with the antidepressants desipramine and paroxetine increased AMPA receptor association with stargazin in rat hippocampus (Martinez-Turrillas *et al*, 2007). Patients with bipolar

disorder or schizophrenia have exhibited decreased CACNG2 DNA copy number (Wilson *et al*, 2006). Yet, increased stargazin mRNA expression has been found in the dorsolateral prefrontal cortex of brains from bipolar disorder patients suggesting a potential regio-specific action for stargazin in this disorder (Silberberg *et al*, 2008). Furthermore, the PDE 11A knockout mouse, which shows multiple psychiatric illness-related phenotypes, possessed decreased hippocampal expression of both γ-2 and -8 proteins (Kelly *et al*, 2010).

Recent research into neuropsychiatric illnesses has shown an emerging pathological role for TARPs. As TARPs are differentially localized in neuron pathways, targeting individual isoforms may enable selective modulation of specific brain circuits without globally affecting synaptic transmission. However, the feasibility of uniquely targeting specific AMPA receptor complexes has not yet been established.

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New Horizons for Selective 5-HT$_{2C}$ Receptor Ligands in Psychiatric/Neurological Disorders

The serotonin (5-HT) 5-HT$_{2C}$ receptor is a key contributor to obesity, autism, psychiatric (eg, depression, schizophrenia), and neurological diseases (eg, Parkinson's disease). The diversity and regulation of the 5-HT$_{2C}$ receptor signaling pathways are complex and provocatively suggest the importance of this receptor in an array of functions and indications. Therapeutic opportunities for both agonist and antagonist compounds that engage this receptor continue to emerge.

The most advanced 5-HT$_{2C}$ receptor agonist in development is lorcaserin, which has completed phase III clinical trials and has submitted an NDA for the treatment of obesity (Pauli and Abdelghany, 2010). In a 12-week obesity trial, approximately 30% of patients at 10 mg b.i.d. showed $>5\%$ weight loss with lorcaserin with minimal adverse events. Earlier in development is another 5-HT$_{2C}$ receptor agonist vabicaserin for the treatment of psychiatric indications. Vabicaserin is a highly selective 5-HT$_{2C}$ agonist (Dunlop *et al*, 2010) with a strong preclinical profile supporting multiple indications. Despite initial concerns regarding potential cardiovascular liabilities, selective 5-HT$_{2C}$ agonists are proving to be devoid of these concerning side effects (Pauli and Abdelghany, 2010).

Many different genetically modified animals have been created to improve understanding of the 5-HT$_{2C}$ receptor. Much of the early work focused on the 5-HT$_{2C}$ receptor knockout mouse that showed a hyperphagic obesity phenotype. However, the 5-HT$_{2C}$ receptor is subject to RNA editing leading to different forms of the receptor that are more (unedited) or less (fully edited) sensitive to the functional effects of 5-HT$_{2C}$ agonists. Therefore, more recently, transgenic animals have been developed that lock the 5-HT$_{2C}$ receptor into a fully edited (VGV) or an unedited (INI) isoform. Interestingly, animals locked into the fully edited VGV form of the receptor show failure to thrive, neonatal muscular hypotonia, decreased somatic growth, and reduced fat mass despite hyperphagia, characteristics consistent with Prader–Willi syndrome (Kawahara *et al*, 2008; Morabito *et al*, 2010). The link between Prader–Willi syndrome and the 5-HT$_{2C}$ receptor has also been made through regulation of the splicing of the 5-HT$_{2C}$ receptor by HBII-52, a small nucleolar RNA that affects 5-HT$_{2C}$ receptor function (Kishore and Stam, 2006). Patients with Prader–Willi syndrome do not express HBII-52 that regulates alternative splicing of the 5-HT$_{2C}$ receptor by binding to a silencing element in exon Vb (Kishore and Stam, 2006). Moreover, these VGV mice have reduced G-protein-coupling efficiency and agonist binding but show enhanced behavioral sensitivity and serotonergic neurotransmission due to increased cell-surface expression of the 5-HT$_{2C}$ receptor (Kawahara *et al*, 2008; Olaghere da Silva *et al*, 2010). Interestingly, both the nonedited INI mice and the fully edited VGV mice show anxiety-like phenotypes with the INI mice showing a depressant-like phenotype and the VGV mice showing an antidepressant-like phenotype (Mombereau *et al*, 2010). Taken together, these transgenic models continue to show the complexity of the regulation of this receptor and the corresponding complexity of phenotypes.

The multitude of ways that the 5-HT$_{2C}$ receptor is regulated through different signaling pathways, RNA editing, and changes in receptor