

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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DISCLOSURE

Both MBG and DSB are employees of Eli Lilly and Company.

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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

expression coupled with its involvement in multiple psychiatric and neurological illness place this receptor as a critical player in the understanding of CNS disorders.

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DISCLOSURE

The author was an employee of Pfizer (formerly Wyeth).

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Modeling Neuropsychiatric Disease-Relevant Human SNPs in Mice

Single nucleotide polymorphisms (SNPs) are variations in DNA sequence that occur when a single nucleotide in the genome is altered. These seemingly small variations can have a major impact on how humans respond to disease, environment, and drugs.

Gene targeting in mice has allowed the analysis of varied aspects of gene

function in mammals. During the past decade, thousands of null, hypomorphic, and conditional alleles have been constructed. Gene targeting can also be used to generate point mutations in mice for those genes in which human SNPs have been identified. This approach, however, has not yet been widely used due, in part, to the labor-intensive procedures involved in building the complex targeting vectors required. Recent advances in ‘recombinering’ of bacterial artificial chromosome vectors have streamlined this process (Yu *et al*, 2000; Lee *et al*, 2001), making the use of ‘knock-in’ mice a natural progression for the development of mouse models to investigate human disease-related SNPs.

Neuropsychiatric diseases are dependent on multiple genetic and environmental determinants, and thus represent some of the greatest challenges for animal modeling. However, a few genes harboring specific SNPs have emerged as promising candidates. Among these, common SNPs in brain-derived neurotrophic factor (*Bdnf*), the μ -opioid receptor (*Oprm1*), and catechol-O-methyltransferase (*COMT*) have been modeled in mice using three unique approaches.

A common SNP in the *BDNF* gene (Val66Met) is associated with anatomical (hippocampal volume) and behavioral (performance in memory tasks) impairments in humans. To recapitulate the equivalent variant in mice, we made a point mutation (G196A) to change valine 66 to methionine. In addition to the expected phenotypes of decreased hippocampal volume and impaired context-dependent memory, these mice revealed a novel anxiety phenotype that had not yet been reported in humans (Chen *et al*, 2006).

A large number of studies have examined the *OPRM1* gene as a candidate for genetic contribution to the risk for substance dependence. The best-characterized polymorphism in this gene is a missense mutation in exon 1, involving an A–G substitution at position 118. Owing to the high sequence similarity between mouse and human at the

nucleotide (86.9%), and amino-acid level (92.3%), a knock-in mouse was developed that possessed the mouse-equivalent SNP of the human A118G SNP in the murine *Oprm1* gene (Mague *et al*, 2009). In a complementary approach, a second mouse line for this SNP was generated that expressed humanized receptors with and without the A118G variant (Ramchandani *et al*, 2010). Both models recapitulated some phenotypes observed in humans, clarified discrepancies regarding functional aspects of the receptor, and identified novel phenotypes.

A third approach to model human SNPs takes advantage of a biochemical phenotype associated with a polymorphism in the *COMT* gene (*COMT-Val*), which results in higher protein levels and enzyme activity compared with individuals expressing *COMT-Met*. However, several other common haplotypes in the *COMT* gene have been associated with similar biochemical effects. Therefore, to model this phenotype and clarify the specificity of the *COMT-Val* SNP, was generated a transgenic mouse that overexpressed the *COMT-Val* gene in the continued presence of the mouse *Comt1* gene (Papaleo *et al*, 2008). Phenotypes related to cognitive and stress reactivity in these transgenic mice were analogous to those reported in humans.

Modeling human SNPs in mice is important for a variety of reasons. In some cases the rationale might be to clarify inconsistencies associated with *in vitro* data, in others to provide more precise information on the specificity of the SNP, or to explore novel phenotypes. In all cases, these mice now allow for the determination of molecular mechanisms that mediate the behavioral consequences of these SNPs, and as such contribute to a better understanding of their significance in human disease.

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