Target Safety Assessment of HTR2C

Sample Report
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<th>Therapeutic benefits</th>
<th>Benefits to risk</th>
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<td>• Modulation of the HTR2C receptor activity is expected to have widespread therapeutic implications affecting appetite &amp; satiety, libido, mood, behavior, sleep, pain perception, insulin sensitivity, glucose homeostasis &amp; susceptibility to seizures/epilepsy.</td>
<td>• The highly conserved ligand binding region and comparable binding affinity of inhibitors among the aminergic GPCRs and closest paralogs HTR2A and HTR2B may lead to off-target effects becoming a potential safety issue. Hence, development of receptor specific drug/agonist is extremely critical. HTR2C is extensively expressed in different regions of brain; its expression in the cervix, muscle, placenta, prostate, and seminal vesicle may lead to direct on-target toxicity in these unintended organs.</td>
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<td>• Marketed agonists of HTR2C, including the moderately selective lorcaserin (trade name Belviq), are typically well-tolerated with manageable adverse effects.</td>
<td>• RNA editing results in receptor isoforms that activate G protein less efficiently, with a possible link to depression and suicide. 5-HT2C pre-mRNA editing and splicing are intertwined processes that determine the receptor activity &amp; expression in pathological conditions.</td>
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<td>• Lorcaserin, an approved drug in obesity, has serotonergic properties and is an appetite suppressant (anorectic). Vabicaserin demonstrated clinical efficacy in a phase II trial in schizophrenia patients without weight gain and with low extrapyramidal side effects (EPS).</td>
<td>• Mice expressing mRNA-edited version of HTR2C having low activity, develop Prader-Willi syndrome with a phenotype associated with failure to thrive, decreased somatic growth, neonatal muscular hypotonia, and reduced food consumption followed by post-weaning hyperphagia.</td>
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<td>• Polymorphisms in HTR2C appear to affect the risk of developing major mental disorders including schizophrenia, bipolar disorder and depression and the propensity to gain weight/hyperphagia. With males having single copy of the gene (in X chromosome) and in females one of the two copies of the gene being repressed, polymorphisms at this receptor can affect the two sexes to differing extent.</td>
<td>• Knock out mice display hepatic insulin resistance; suggesting agonists may have therapeutic benefit in type II diabetes, while antagonists could exacerbate the condition.</td>
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<td>• A risk of depression/suicide intention is associated with cytokine therapy in the treatment of viral infections and certain malignancies including glioblastoma. This could be attributed to HTR2C receptor hypoactivity due to dysregulated mRNA editing by activated ADAR1, downstream of hIFNα activation, as a response to infection.</td>
<td>• 5-HT2C protein expression is reported to be important for embryonic brain development and its presence is detected throughout the gestation period in rats. Therefore, the use of psychotropic drugs during pregnancy may have an adverse effect on HTR2C mediated brain development.</td>
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II. Target biology relevant to toxicology

**Function and pathology**

The HTR2C gene encodes a seven-transmembrane G-protein-coupled receptor. The 5-HT2C receptor is one of the receptors for serotonin (5-hydroxytryptamine), activation of which inhibits dopamine and norepinephrine release in certain areas of the brain. This further modulates the activity of down-stream effectors (Knauer et al., 2009; Cussac et al., 2008; De Deurwaerdère et al., 2017). Upon binding to serotonin, the 5-HT2C receptor mediates the release and increase of extracellular dopamine in response to drugs (Esposito, 2006; Bubar and Cunningham, 2006).

- Serotonin mediated over-activation of 5-HT2C has been reported to contribute to depressive and anxiety symptoms in certain patient populations. In some patients, treatment with SSRI (selective serotonin reuptake inhibitor) or SNRI (serotonin and norepinephrine reuptake inhibitors) also leads to anxiety initially, believed to be mediated by excessive receptor signaling. However, over time, these symptoms resolve as HTR2C, HTR2A and other homologs begin to downregulate.

- 5-HT2C is widely implicated in the etiology of affective and eating disorders as well as regulation of the hypothalamo-pituitary-adrenal axis (Bombail et al., 2014).

- **5-HT2C antagonism increases dopamine release** in response to reinforcing drugs, and many dopaminergic stimuli. Blocking of 5-HT (serotonin) to receptor decreases neuron firing to the limbic circuits, in the frontal cortex. Blocking 5-HT2C therefore increases dopamine and norepinephrine levels which exert anti-depression and anxiolytic actions in patients with behavioral problems. 5-HT2C is involved in spinal cord injury-induced spasms of the lower limbs; the condition gets better by 5-HT2C antagonists/inverse agonists treatment.

- **5-HT2C agonism causes increased intracellular inositol triphosphate & cytosolic Ca²⁺**; it activates upstream of corticotrophin-releasing hormone (CRH) signaling system. This activation plays a role in the regulation of appetite and eating behavior, responses to anxiogenic stimuli and stress, insulin sensitivity and glucose homeostasis.

(Millan et al., 2008; McGrew et al., 2004; Chang et al., 2000; Di Matteo et al., 2001; Esposito, 2006; Heisler et al., 2007; Bubar et al., 2011; Palacios et al., 2017)

Receptor function in orthologs (mouse, rat, rhesus and cynomolgus) include core CNS functions e.g. mood, cognition, sleep, pain, motor function and endocrine secretion as in human along with embryonic brain development in mouse (Mengod et al., 1990; Tanaka et al., 2012; LópezGiménez et al., 2001; Li et al., 2004; Lauder et al., 2010).

Selective post-transcriptional mRNA-editing could be involved in the pathophysiology of psychiatric disorders through impairment in G-protein interactions. It may further influence the therapeutic response atypical antipsychotic drugs. In addition, 5-HT2C exhibits alternative splicing. They are often linked to pathology of several human mental conditions such as schizophrenia, anxiety, bipolar disorder and major depression (Nikolaus et al., 2016; Chagraoui et al., 2015).

- Clinically relevant behavioral changes are associated with alterations in mRNA editing, splicing and receptor density (expression) in depression and suicide (Martin et al., 2013; Pantazatos et al., 2017); in conjunction with decreased brain 5-HT turnover.
mRNA editing

RNA editing affects three amino acids which gets reflected in the protein sequence. Unedited transcripts, encoding a full-length receptor (IN1), is hyperactive (with considerable constitutive and agonist-stimulated activity) compared with edited isoforms in vitro (Bombail et al., 2014). Multiple RNA editing events occur within exon 5, in five different closely located sites (namely A, B, E (C'), C and D) in human. This editing is reported to be associated with the alteration of the receptor ability to activate phospholipase C (Kegg). This further regulated food consumption and appetite by promoting satiety via appetite suppression (Flomen et al., 2004; Chagraoui et al., 2016; OMIM). These sites in mRNA correspond to the second intracellular loop of the fully folded protein. Combinatorial editing at the five positions can generate up to 32 mRNA variants encoding 24 different receptor isoforms with varied receptor function (Doe et al., 2009). Adenosine residues encoded by the genome are converted to inosines by interferon-inducible editing enzyme ADAR1s (Liu et al., 1999; Schmauss et al., 2010). HTR2C is the only serotonin receptor as well as the only member of the large family of 7 transmembrane receptors (7TMRs) that are known to be edited. Many 5-HT2CR edited variants exist, especially in humans, in addition to a few 5-HT2CR splice variants.

To know more about Syngene’s Target Safety Assessment services, contact us at bdc@syngeneintl.com