Serotonin Receptor Profiles of Bedtime Pharmacotherapies Targeting Posttraumatic Stress Disorder (PTSD)

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Abstract 728

Introduction

- Syndromal sleep disturbances in PTSD are targeted by drugs that antagonize serotonin (5-HT) receptors, particularly 5-HT1A and 5-HT2C.
- Several lines of evidence implicate antagonism of 5-HT1A and 5-HT2C receptors in the enhancement of slow wave sleep (SWS), the type of sleep often referred to as restorative sleep.
- Cyclobenzaprine (CBP) and trazodone (TZD) are bedtime PTSD treatment candidates with several 5-HT receptor-mediated actions, and both have major metabolites that are differentially active at 5-HT receptors.
- meta-chlorophenylpiperazine (mCPP), the major metabolite of TZD, at 1 mg/kg i.v. produces flashbacks, panic attacks and exacerbates other PTSD symptoms in about a third of patients with combat PTSD.
- In this work, the activities of CBP and TZD, and their respective metabolites norcyclobenzaprine (nCBP) and mCPP, on human 5-HT receptors were investigated.

Methods

Radiolabeled binding assays
- Receptor binding assays were performed under equilibrium conditions on Chinese hamster ovary (CHO) cell membranes expressing the various recombinant human receptors.
- Binding of 1H-labeled ligands specific for each receptor were carried out in the presence of varying concentrations of unlabeled compounds using standard procedures (Eurofins Scientific, France).
- Inhibition constants (K_i) were calculated using the Cheng-Prusoff equation (K_i = IC50 / (1 + [L]/K_m)), where L = concentration of radioligand, and K_m = affinity for the receptor.

Ligand-induced calcium mobilization assays
- Rat basophilic leukemia (RBL) cells expressing the various recombinant human receptors were evaluated for agonist and antagonist activity of the various compounds in ligand-induced calcium mobilization using standard procedures (Eurofins Scientific, St. Charles, MO).
- Maximum values were converted to percent activation (relative to reference agonist and vehicle control values) and percent inhibition (relative to vehicle control values).

The Liver Transforms Cyclobenzaprine and Trazodone to Active Metabolites

Cyclobenzaprine (CBP) is metabolized by hepatic p450 isozymes into the active metabolite norcyclobenzaprine (nCBP).

Trazodone (TZD) is metabolized by hepatic p450 isozymes into the active metabolite meta-chlorophenylpiperazine (mCPP).

Cyclobenzaprine Has Moderate to High Binding Affinities on Multiple Receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>CBP</th>
<th>nCBP</th>
<th>Trazodone</th>
<th>mCPP</th>
<th>Prazosin</th>
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<tbody>
<tr>
<td>5-HT1A</td>
<td>230</td>
<td>140</td>
<td>470</td>
<td>79</td>
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<td>5-HT1B</td>
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<td>580</td>
<td>3000</td>
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<td>5-HT2C</td>
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<td>1220</td>
<td>No Activity</td>
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<tr>
<td>α1A</td>
<td>5.2</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>360</td>
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<td>SERT</td>
<td>39</td>
<td>32</td>
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</table>

Cyclobenzaprine Shows a Balanced Binding Profile

Cyclobenzaprine Can Act Through Dual Signaling Pathways

Cyclobenzaprine Combines Activities of Trazodone & Prazosin, Plus NET Inhibition

Conclusions

Cyclobenzaprine is a Serotonin and Norepinephrine receptor Antagonist and Reuptake Inhibitor (SNARI)
- CBP has potent antagonist activity at 5-HT1A, 5-HT2C, and NET receptors.
- 5-HT1A antagonist activity of CBP is in common with TZD, commonly used for sleep effects in psychiatric conditions, including off-label use in PTSD.
- α1A antagonist activity of CBP is in common with prazosin, commonly used off-label to treat night terrors and sleep disturbance in PTSD.
- CBP is metabolized into the active metabolite nCBP, which is a stronger NET inhibitor and has a similar binding profile to CBP, albeit with less potency.
- TZD is metabolized into the active metabolite mCPP, an agonist at 5-HT1C (suspected to cause panic- and flashback-inducing effects in combat PTSD).
- The lack of 5-HT1C agonist effects of it or its metabolite makes CBP a promising candidate for clinical trials of bedtime therapy targeting sleep disturbance for improving daytime symptoms of PTSD.
- As noted by Jonathan Davidson, “Opportunities exist to reassess the efficacy and safety of TCAs (for PTSD).” Examples in support of this contention include the use of low-dose, cyclobenzaprine.
- Tonix is currently conducting a Phase 2 study to investigate the efficacy and safety of low-dose, sublingual CBP for the treatment of military-related PTSD (ClinicalTrials.gov Identifier: NCT02277704).

References