**Comparative Neuropharmacology of Therapeutic Agents Targeting Posttraumatic Stress Disorder**

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**Introduction**

• Radiolabeled binding assays in PTSD are targeted by drugs that antagonize 5-HT receptors, particularly 5-HT₂A and 5-HT₃ receptors, and adrenergic alpha-1 receptors.

• Several lines of evidence implicate antagonism of 5-HT₂A and 5-HT₃ receptors in the enhancement of slow wave sleep (SWS), the type of sleep often referred to as restorative sleep.

• Cyclobenzaprine (CBP) and trazodone (TZD), prazosin on human receptors were investigated.

• In this work, the activities of CBP and TZD, their respective metabolites, norcyclobenzaprine (nCBP) and metabolite, were evaluated on 5-HT receptors.

**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 radiolabeled ligands specific for each receptor were carried out in the presence of varying concentrations of unlabeled compounds using standard procedures (Eurofins Scientific, St. Charles, MO).

• Inhibition constants (Kᵢ) were calculated using the Cheng-Prusoff equation (Kᵢ = IC₅₀ × KᵦL / (IC₅₀ + KₐL)), where IC₅₀ is the concentration of radioligand, and Kᵦ is affinity for the receptor.

Ligand-induced calcium mobilization assays

• Radiolabeled calcium mobilization was measured in CHO cell lines expressing the various recombinant human receptors.

• Maximum values were corrected by 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

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

CBP is metabolized by hepatic p450 isozymes into the active metabolite mCPP.

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

**Cyclobenzaprine Has Moderate to High Binding Affinities on Multiple Receptors**

• Cyclobenzaprine has moderate to high binding affinities on multiple receptors.

• The size of the receptor icon is proportional to its activity on that receptor.

- **Cyclobenzaprine**
  - 5-HT₂A Antagonism
  - 5-HT₂B Antagonism
  - 5-HT₂C Antagonism
  - 5-HT₂D Antagonism
  - 5-HT₃A Agonist
  - 5-HT₃B Agonist
  - 5-HT₃C Agonist
  - 5-HT₃D Agonist
  - SERT Antagonist
  - α₁A Agonist
  - α₁B Agonist
  - α₁C Agonist
  - α₁D Agonist
  - H₁ Antagonist
  - NET Antagonist

- **Trazodone**
  - 5-HT₂A Agonist
  - 5-HT₂B Agonist
  - 5-HT₂C Agonist
  - 5-HT₂D Agonist
  - 5-HT₃A Agonist
  - 5-HT₃B Agonist
  - 5-HT₃C Agonist
  - 5-HT₃D Agonist
  - SERT Antagonist
  - α₁A Agonist
  - α₁B Agonist
  - α₁C Agonist
  - α₁D Agonist
  - H₁ Antagonist
  - NET Antagonist

**Cyclobenzaprine Can Act Through Dual Signaling Pathways**

**Signaling in Neurons**

- Serotonin (S)
  - Neuron
  - Serotonin (S)
  - Neuron

**Effects of Trazodone and Prazosin**

- Trazodone
  - SERT
  - Neuropharmacology
  - Prazosin
  - Neuropharmacology

**Cyclobenzaprine Combines Activities of Trazodone & Prazosin, Plus NET Inhibition**

- Trazodone
  - SERT
  - Neuropharmacology
  - Prazosin
  - Neuropharmacology
  - NET Inhibition

**Conclusions**

- Cyclobenzaprine is a Serotonin and Norepinephrine receptor Antagonist and Reuptake Inhibitor (SNAMI).
  - CBP receptor antagonism effects of 5-HT₂B, 5-HT₂C, and α₁A receptors.
  - α₁B receptor antagonism of CBP in common with TZD is considered to be an off-target effect on SWS.
  - Cyclobenzaprine has antidepressant effects of CBP 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 strong NET inhibitor and has a similar binding profile to CBP, albeit with less potency.
  - TZD and CBP are considered to have similar activities on both CBP and TZD are considered to be off-label use in PTSD.
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**References**