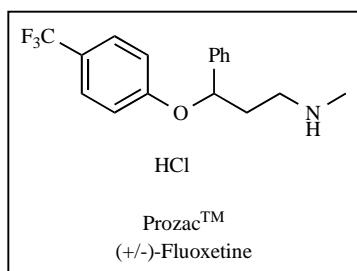


Molecule of the Month

A new, non-SSRI mechanism of action for ProzacTM. Unquestionably, ProzacTM was a landmark drug that redefined the treatment for depression, anxiety disorders, premenstrual syndrome and post-traumatic stress disorder as well as ushering in a wave of new therapies targeting specific serotonin (5-HT) reuptake inhibition (SSRI) [1]. In a recent manuscript (*Psychopharmacology* **2006**, *186*, 362-372), Pinna and co-workers report that fluoxetine and its *N*-desmethyl congener norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake [2]. Pinna further states that the term 'SSRI' may be misleading in describing the pharmacological profile of fluoxetine and its congeners and suggests the term 'selective brain steroidogenic stimulants' (SBSSs) as a better descriptor [2].



Recently, it has been shown that neurosteroids, such as allopregnanolone (Allo), play critical roles in human brain pathophysiology such as anxiety disorders, premenstrual syndrome, post-traumatic stress disorder, postpartum depression and general depression. For the treatment of major depression, recent clinical trials have indicated that the pharmacological profiles of ProzacTM and related congeners correlate with an increase of Allo in the brain and cerebrospinal fluid. Importantly, Allo is a potent (nM affinity) positive allosteric modulator of gamma-aminobutyric acid (GABA) action at GABA_A receptors, potentiating the intensity of GABA-gated Cl⁻ currents [3]. Thus, ProzacTM and related analogs increase Allo levels, and subsequent activation of GABA_A receptors, at currently prescribed clinical doses which may not block 5-HT reuptake, but does effectively treat depression, premenstrual dysphoria and anxiety [2].

Pinna then explored this hypothesis in animal behavioral models of aggression and anxiety [2]. Their studies found that

social isolation in mice is correlated with a down-regulation of Allo content and that pretreatment with Allo abolished aggressiveness as well as correcting the altered responses of GABA_A receptors to specific agonists (pentobarbital) and antagonists (picrotoxin). Therefore, drugs capable of upregulating brain Allo content normalize behavioral abnormalities expressed in mice with a down-regulation of brain Allo levels. Significantly, Pinna and co-workers discovered that the actions of fluoxetine and norfluoxetine on brain Allo content are stereoselective whereas 5-HT reuptake lacks stereospecificity. ProzacTM is a racemic compound. Pinna found that the EC₅₀s of the (S)-enantiomers of fluoxetine and norfluoxetine to normalize brain Allo levels are 10- and 50-fold lower than those required to inhibit 5-HT reuptake [2]. Will this research herald new drug discovery campaigns aimed at identifying compounds capable of selectively increasing brain Allo levels under the moniker SBSSs?

REFERENCES

- [1] Wong, D.T.; Bymaster, F.P.; Reid, L.R.; Mayle, D.A.; Krushinski, J.H.; Robertson, D.W. Norfluoxetine enantiomers as inhibitors of serotonin uptake in rat brain. *Neuropsychopharmacology* **1993**, *8*, 337-344.
- [2] Pinna, G.; Costa, E.; Guidotti, A. Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. *Psychopharmacology* **2006**, *186*, 362-372.
- [3] Lambert, J.J.; Belelli, D.; Peden, D.R.; Vardy, A.W.; Peters, J.A. Neurosteroid modulation of GABA_A receptors. *Prog. Neurobiol.* **2003**, *71*, 67-80.

R. Nathan Daniels
Craig W. Lindsley

Vanderbilt University, Vanderbilt University Medical Center
Associate Professor of Pharmacology and Chemistry
Robinson Research Building 804
Nashville, TN 37232-6600,
USA