ACS Chemical Neuroscience

In This Issue

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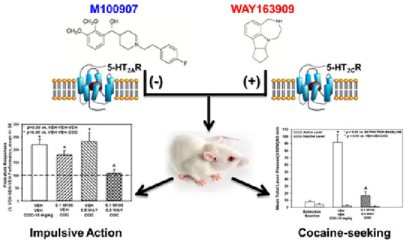
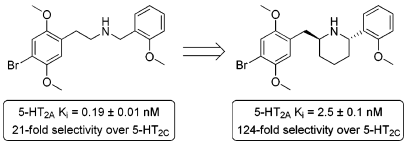
ALLEVIATING COCAINE ADDICTION



Cocaine-dependence comes with chronic psychological and physical burdens. Due to liability factors associated with impulsivity and cue reactivity, former cocaine users are susceptible to relapse even after years of abstinence. New and more effective treatments for the long-term management of cocaine addiction are needed. Previous studies have shown that serotonin plays a role in these liability factors through its interactions with two types of serotonin receptors, 5-HT_{2A} receptors (5-HT_{2A}Rs) and 5-HT_{2C} receptors (5-HT_{2C}Rs). In the current issue, Cunningham et al. (DOI: 10.1021/cn300072u) investigate animal models of cocaine addiction to understand further how relapse occurs.

Their research shows that by inhibiting 5-HT_{2A}Rs, while simultaneously promoting the activity of 5-HT_{2C}Rs, impulsive behavior and reactivity to cocaine-associated cues can be reduced. Moreover, effects at these two receptor subtypes are synergistic, and low doses of drugs that are ineffective alone modify behavior when administered together. This information is important for the rational design of new medications with the promise to restore normal neural function in cocaine-dependent individuals. (See also *ACS Chemical Neuroscience* DOI: 10.1021/cn300020x and DOI: 10.1021/cn200077q.)

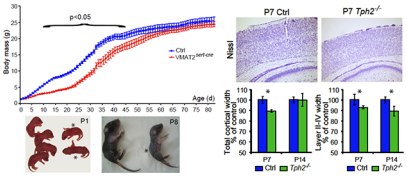
DEVELOPMENT OF SELECTIVE SEROTONIN 5-HT_{2A} RECEPTOR LIGANDS



In addition to its role in cocaine addiction, 5-HT_{2A} receptors are believed to be primary targets of psychedelics and to mediate the action of atypical antipsychotics (along with 5-HT_{2C} receptors). 5-HT_{2A} receptors are also linked to learning processes and, in particular, those associated with long-term drug use. In the current issue, Juncosa et al. (DOI: 10.1021/cn3000668) develop more potent and selective agonists for 5-HT_{2A} receptors, which have historically been difficult to differentiate pharmacologically from 5-HT_{2C}Rs.

The authors synthesized a series of constrained analogues based on the structure of *N*-benzylphenylethylamine, a known 5-HT_{2A} receptor agonist. One analogue showed a >100-fold increase in selectivity for 5-HT_{2A} receptors over 5-HT_{2C} receptors. This specificity is considerably higher than that previously observed and provides further impetus for the development of potential therapeutics.

CORRELATION BETWEEN SEROTONIN LEVELS AND POSTNATAL GROWTH DEFECTS

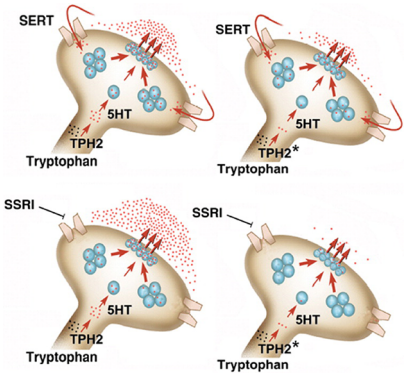


Genetically modified animals offer powerful avenues to explore the consequences of changes in gene expression. In the current issue, Narboux-Nême et al. (DOI: 10.1021/cn300165x) describe alterations in the development of the body and brain in transgenic mice with central nervous system serotonin (5-hydroxytryptamine; 5-HT) deficits.

The authors present data on postnatal growth and cortical development in three mutant mouse lines. These strains exhibit lifelong reductions in brain serotonin levels via different mechanisms. In one mouse model, the rate-limiting enzyme for serotonin synthesis in the brain, tryptophan hydroxylase 2 (TPH2), is genetically inactivated (*Tph2*$^{-/-}$ mice). In the other two models, the gene coding for the vesicular monoamine transporter 2 (*Slc18a2*) is inactivated under the control of two different promoters (VMAT2^{SERTCre} and VMAT2^{Pet1Cre} mice). Serotonin is sequestered into synaptic vesicles in brain neurons by vesicular monoamine transporters type 2 (VMAT2) prior to release.

Postnatal growth retardation varied according to the extent of brain serotonin reductions, while embryonic growth was spared. Furthermore, morphological analysis revealed delayed maturation of the upper layers of the cortex in the brains of mice with the greatest serotonin reductions, that is, VMAT2^{SERTcre} and *Tph2*$^{-/-}$ mice. Convergent findings across mouse lines clarify understanding of the role of serotonin in brain and somatic growth during postnatal development.

CAUTION WHEN USING SSRI INHIBITORS TO TREAT DEPRESSION



Serotonin-selective reuptake inhibitors (SSRIs) are the most widely prescribed pharmacological treatment for depression

Special Issue: Celebrating 25 Years of the Serotonin Club

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and anxiety disorders. In the current issue, Siesser et al. (DOI: 10.1021/cn300127h) show that tryptophan hydroxylase 2 (TPH2), the enzyme responsible for serotonin synthesis, is essential for maintaining serotonin homeostasis during chronic treatment with SSRIs.

Mice genetically engineered to express a rare human *TPH2* mutation have only 20% of normal serotonin tissue levels. Repeated administration of SSRIs further exacerbates this reduction, demonstrating that SSRI treatment may lead to a pronounced depletion of serotonin levels. Thus, SSRI administration may worsen depressive symptoms in patients carrying *TPH2* polymorphisms that result in low enzyme activity. The authors further show that the serotonin precursor, 5-hydroxytryptophan, rescues levels of serotonin in *Tph2* mutant mice and can prevent the depleting effects of chronic SSRIs. These findings have clinical implications for personalizing treatments for individuals suffering from depression.