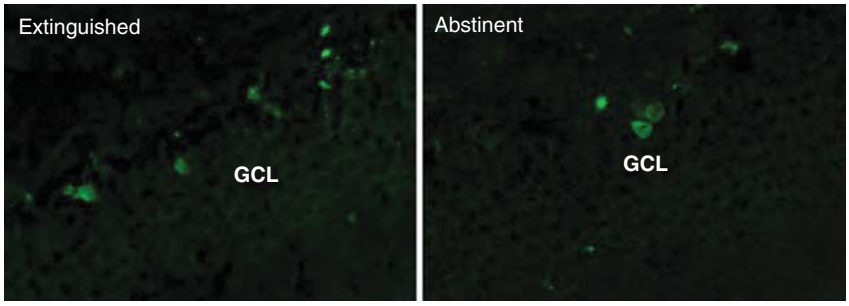

Figure 1. Rats self-administered heroin 3 h daily for 12 days and were then administered 2-bromodeoxyuridine (BrdU) immediately after the first five extinction training sessions or the on first 5 days of forced abstinence. Extinction-trained animals (left) showed approximately twice as many BrdU-labeled cells in the subgranular layer as those that underwent forced abstinence (right). GCL, granule cell layer.

adult-born neurons may be involved in certain learning and memory processes.

As extinction is a form of learning, it would follow that adult hippocampal neurogenesis (AHN) might have a role in extinction processes. An initial study showed that ablation of AHN in mice by γ-irradiation or anti-mitotic agent administration failed to affect the extinction of contextual fear memory (Ko *et al*, 2009). However, it was subsequently showed that conditional ablation of AHN in a nestin-thymidine kinase transgenic mouse line indeed impaired extinction of a contextual fear memory (Deng *et al*, 2009). In agreement with these latter findings, disruption of AHN by irradiation impaired the extinction of cocaine-seeking behavior in rats following intravenous cocaine self-administration (Noonan *et al*, 2010).

Performance of various learning and memory tasks can increase AHN, further supporting a role for these neurons in experience-dependent neural plasticity. To this end, extinction training following intravenous heroin self-administration increases cell proliferation in the hippocampus (Figure 1; see also Wischerath *et al*, 2009), and in agreement with the observations of Noonan *et al* (2010), conditional ablation of AHN in mice impairs extinction learning following heroin self-administration (unpublished observations). Together, these data suggest that in most instances, AHN is involved in extinction learning, and future studies are needed to determine the precise environmental conditions as well as the chemical and molecular regulators of AHN. As a result, AHN could potentially be targeted as an adjunct to extinction-based therapies, such as cue exposure therapy, that are used in the treatment of anxiety and substance use disorders.

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Transcriptional Control of Serotonin-Modulated Behavior and Physiology

Altered levels of serotonergic activity have been linked to the pathogenesis of numerous neurological and psychiatric disorders such as autism, sudden infant death syndrome (SIDS), depression, and anxiety. These alterations are thought to cause abnormal formation of neural circuitry responsible for the development and expression of adaptive behaviors and physiological processes. How might these alterations be brought about? Genetic variation in or near genes encoding the serotonin (5-HT) reuptake transporter, *5-HT$_{1A}$* receptor, and the rate-limiting synthetic enzyme tryptophan hydroxylase 2 is associated with risk for behavioral pathogenesis (Holmes, 2008). Functional studies in cell culture suggest that some of the identified variants alter levels of gene transcription.

These findings raise an alternative potential mechanism underlying behavioral pathogenesis in which variation in serotonergic gene transcription causes altered levels of serotonergic activity. As many of the disorders in which serotonergic dysfunction has been implicated are neurodevelopmental in origin, altered function of the transcriptional programs that control 5-HT neuron generation may establish a vulnerability for pathogenesis by directing abnormal levels of serotonergic signaling that in turn disrupt neural circuit formation during critical periods in early life.

Over the past decade, transcriptional cascades that program the generation of 5-HT neurons have been identified. Gene targeting of individual cascade factors has created specific deficiencies in serotonergic transcription at a stage when CNS neural circuitry has not yet formed (Hendricks *et al*, 2003; Zhao *et al*, 2006). These studies show that all of the cascade factors are necessary for the initiation of 5-HT synthesis.

Furthermore, rescue experiments in cascade-disrupted mice show that the level of serotonergic function is sensitive to the level of expression of the transcriptional program that gives rise to 5-HT neurons (Lerch-Haner *et al*, 2008).

The irreversible alterations in brain serotonergic transcription are not lethal and therefore cascade-targeted mice provide a new way to investigate the impact of altered serotonergic function on animal behaviors and physiological processes that are relevant to many psychiatric and neurological disorders. Indeed, disruption of the serotonergic transcriptional cascade causes alterations in emotional behaviors (Hendricks *et al*, 2003). In addition, these approaches have provided experimental support, *in vivo*, for the hypothesis that abnormal serotonergic development contributes to SIDS vulnerability (Erickson *et al*, 2007; Hodges *et al*, 2008). They have also revealed maternal nurturing as a previously unrecognized 5-HT system-modulated behavior (Lerch-Haner *et al*, 2008). The accompanying high mortality rate of offspring born to cascade-targeted mothers forces a reassessment of the long-held view that the brain 5-HT system is not essential for physiological processes and animal survival.

The new genetic approaches created to study 5-HT neuron development and function support the idea that altered transcriptional programming of serotonergic signaling is a potential mechanism underlying behavioral and physiological pathogenesis. Future studies might be focused on determining the vulnerability of cascade activity to fetal and early postnatal exposure to environmental insults such as drugs and harmful stress. In addition, the identification of genetic variation that impacts cascade factor activity may reveal additional 5-HT-related risk factors for pathogenesis beyond the usual suspects.

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An Emerging Role for TARPs in Neuropsychiatric Disorders

The discovery of glutamate as the principal excitatory neurotransmitter in brain was followed by the identification and molecular cloning of the ionotropic glutamate receptor family, which comprises NMDA, AMPA, and kainate receptors. The AMPA receptor subfamily mediates fast synaptic neurotransmission important to diverse sensory, behavioral, and cognitive processes, including learning and memory. However, excessive AMPA receptor activity and subsequent excitotoxicity underlie central nervous system disorders ranging from stroke to epilepsy. It was hypothesized that the development of AMPA receptor antagonists to dampen aberrant neurotransmission would provide treatments for neurological illnesses. However, clinical trials have shown side effects for these antagonists and suggested a need for greater selectivity.

A seminal finding in AMPA receptor biology and neurotransmission was the discovery of stargazin, the protein mutated in stargazer mice, which show absence epilepsy and cerebellar ataxia. Cell biological and physiological studies showed that stargazin is an AMPA receptor auxiliary subunit and controls receptor trafficking, gating, and pharmacology. Subsequent studies have identified a family of related transmembrane AMPA receptor regulator proteins (TARPs). TARPs comprise γ-2 (stargazin), -3, -4, -5, -7, and -8 subunits, which are discretely distributed in specific neuronal and glial populations throughout the brain. Studies involving γ-8 knockout mice, which exhibit deficiencies in hippocampal neurotransmission, underscore the importance of TARPs both in region-specific control of AMPA receptor signaling, and in neurological disease—hippocampal excitotoxicity elicited by the AMPA receptor partial agonist, kainate, is abrogated in γ-8 knockout mice (Tomita *et al*, 2007).

Neuropsychiatric conditions such as schizophrenia, depression, and bipolar disorder are severe, multifactorial brain illnesses of mood, cognition, and behavior whose etiologies remain uncertain. Molecular analyses have found abnormal expression for key components of glutamatergic neurotransmission, including TARPs. Increased and decreased stargazin mRNA expression has been documented in post-mortem schizophrenic and major depressive disorder brains, respectively (Beneyto and Meador-Woodruff, 2006). Silberberg *et al* (2008) found certain *CACNG2* (the gene that encodes stargazin) allelic polymorphisms are associated with improved response to lithium, the classical treatment for bipolar disorder. Furthermore, chronic treatment with the antidepressants desipramine and paroxetine increased AMPA receptor association with stargazin in rat hippocampus (Martinez-Turrillas *et al*, 2007). Patients with bipolar