novel target for antidepressant drugs and offers a new strategy for treatment of depression.

Taken together, GPCR heteroreceptor complexes and their receptor–receptor interactions represent a new fundamental principle in molecular medicine for integration of transmitter signals in the plasma membrane. A novel understanding of the molecular basis of CNS diseases is given together with new strategies for their treatment by targeting heteroreceptor complexes based on a new pharmacology with combined treatment, multi-targeted drugs and heterobivalent drugs. Our perspective on the future of research on heteroreceptor complexes is the further development and employment of multiple techniques for use in cellular models, brain tissue and *in vivo* studies to understand their role in discrete brain circuits. The advancement of the proximity ligation assay will be of special importance as will be the development of selective heterobivalent compounds for the heterocomplexes.

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Borroto-Escuela DO, Perez-Alea M, Narvaez M, Tarakanov AO, Mudo G, Jimenez-Beristain A *et al* (2015). Enhancement of the FGFR1 signaling in the FGFR1-5-HT1A heteroreceptor complex in midbrain raphe 5-HT neuron systems. Relevance for neuroplasticity and depression. *Biochem Biophys Res Commun* **463**: 180–186.

Fuxe K, Borroto-Escuela DO, Romero-Fernandez W, Palkovits M, Tarakanov AO, Ciruela F *et al* (2014). Moonlighting proteins and protein-protein interactions as neurotherapeutic targets in the G protein-coupled receptor field. *Neuropsychopharmacology* **39**: 131–155.

George SR, Kern A, Smith RG, Franco R (2014). Dopamine receptor heteromeric complexes and their emerging functions. *Prog Brain Res* **211**: 183–200.

Guo W, Urizar E, Kralikova M, Mobarec JC, Shi L, Filizola M *et al* (2008). Dopamine D2 receptors form higher order oligomers at physiological expression levels. *EMBO J* **27**: 2293–2304.

Han Y, Moreira IS, Urizar E, Weinstein H, Javitch JA (2009). Allosteric communication between protomers of dopamine class A GPCR dimers modulates activation. *Nat Chem Biol* **5**: 688–695.

Portoghese PS (1992). Edward E. Smissman-Bristol-Myers Squibb Award Address. The role of concepts in structure-activity relationship studies of opioid ligands. *J Med Chem* **35**: 1927–1937.

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Hippocampal Neurogenesis and Memory Clearance

We are constantly forgetting. For a moment, consider what you have done today. It might be relatively straightforward, for example, to recall your journey to work. Similarly, you might recall easily the people you encountered and conversations you had, even with a fair degree of clarity. We keep a good record of these ordinary, everyday events. But what about memories of similar, everyday activities that occurred a week ago? Or a month or a year ago? Unless something extraordinary occurred, it is unlikely that you can recall much of what happened, and certainly not in any great detail. This reflects the fact that while we are continuously encoding our experiences, the vast majority of these encoded experiences (or memories) are 'cleared away' and only a small portion ultimately retained. The hippocampus is thought to be the automatic encoder, with the cortex serving as the final repository for the fraction of memories that are successfully consolidated (Wang and Morris, 2010). But how are memories cleared from the hippocampus?

Recent work has identified one likely clearance mechanism. In the hippocampus, new cells are continuously generated in the subgranular zone of the dentate gyrus. Most of these new cells differentiate into granule cells and migrate into the granule cell layer, where, after a few weeks, they synaptically integrate into the hippocampal circuitry. There has been plenty of interest in how these newly generated neurons might facilitate the formation of new memories (eg, by increasing the mnemonic capacity or facilitating certain types of computations carried out by the dentate gyrus, such as pattern separation) (Christian *et al*, 2014). However, as new cells integrate into the hippocampus they necessarily remodel existing circuitry. This remodeling may degrade memories already stored in those circuits (or at least render them difficult to access) (Deisseroth *et al*, 2004; Weisz and Argibay, 2012). We recently provided experimental support for this prediction (Akers *et al*, 2014). Voluntary exercise increases hippocampal neurogenesis in adult mice. We found that running-induced increases in neurogenesis led to forgetting of established contextual fear and spatial memories. While running induces a number of physiological changes, the forgetting effects appeared to depend on elevated neurogenesis, since genetically attenuating this consequence of running prevented forgetting. Furthermore, pharmacological (eg, memantine, fluoxetine) and genetic (conditional deletion of p53 from neural progenitors) interventions that artificially elevate hippocampal neurogenesis, when introduced after training, similarly weakened existing hippocampus-dependent memories, suggesting that running-induced forgetting is mediated by a neurogenic mechanism.

There are two important implications of these findings. First, not only do they tell us about how forgetting normally occurs, but perhaps additionally they hint at an important functional consequence of ongoing neurogenesis in the adult hippocampus. Established memories interfere with encoding of new memories, especially when the new and established memories are in conflict with one another. By continuously clearing hippocampal memories, ongoing neurogenesis may serve to minimize this form of proactive interference

(Frankland *et al*, 2013). Second, these findings identify a mechanism that could be targeted in memory-related disorders. For example, inefficient neurogenesis-mediated clearance may contribute to human disorders characterized by problems with memory interference (eg, in old age and Alzheimer's disease) or rumination (eg, in PTSD and depression). Interestingly, stress may compound these conditions by further lowering the rates of ongoing neurogenesis.

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Akers KG, Martinez-Canabal A, Restivo L, Yiu AP, De Cristofaro A, Hsiang HL *et al* (2014). Hippocampal neurogenesis regulates forgetting during adulthood and infancy. *Science* **344**: 598–602.

Christian KM, Song H, Ming GL (2014). Functions and dysfunctions of adult hippocampal neurogenesis. *Annu Rev Neurosci* **37**: 243–262.

Deisseroth K, Singla S, Toda H, Monje M, Palmer TD, Malenka RC (2004). Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* **42**: 535–552.

Frankland PW, Kohler S, Josselyn SA (2013). Hippocampal neurogenesis and forgetting. *Trends Neurosci* **36**: 497–503.

Wang SH, Morris RG (2010). Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation. *Annu Rev Psychol* **61**: 49–79 (C41–C44).

Weisz VI, Argibay PF (2012). Neurogenesis interferes with the retrieval of remote memories: forgetting in neurocomputational terms. *Cognition* **125**: 13–25.

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Translational Studies of Sex Differences in Sensitivity to Opioid Addiction

The rapid escalation of opioid addiction, fueled by the increased potency and availability of prescription opioid painkillers, has been declared an epidemic in the US. Although opioid addiction has historically exhibited a substantially higher prevalence in men, adolescent girls are now abusing opioids at a higher rate than boys, the prevalence of fatal opioid overdoses has increased at a higher rate among women relative to men, and women are more likely to use opioids to manage stress. This commentary highlights three examples of recent advancements and ongoing challenges in translational studies of sex differences in sensitivity to the addictive properties of mu opioid receptor (MOR) agonists such as morphine, oxycodone and heroin.

One recent advancement in mechanistic understanding of these sex differences is the finding in *ex vivo* hippocampal slice preparations that a form of MOR-dependent cellular learning is dramatically enhanced in proestrous female rats, when 17-β estradiol levels are at their peak (Harte-Hargrove *et al*, 2015). This female-specific, estradiol-dependent lowering of thresholds for synaptic plasticity may explain, in part, why female rats with high estradiol levels acquire opioid self-administration behavior more rapidly than males (Roth *et al*, 2002). Although these findings mirror the observed 'telescoping' course of illness in women relative to men—characterized by a more rapid progression from initiation of opioid use to an opioid use disorder—there is not direct clinical evidence that estradiol contributes to the telescoping effect.

In a second example, a mouse model of the human MOR A118G SNP replicates many of the phenomena observed in human variants, including reduced morphine analgesia in G allele carriers. But detailed studies of the mouse model also demonstrate that G/G females are significantly less sensitive than A/A females to morphine reward and withdrawal-induced negative affective states, whereas males exhibit similar responses to morphine regardless of allele status (Mague *et al*, 2009). These types of sex by gene interactions, which can have profound effects on addiction risk, are an important future direction in human association studies.

As a final example, recent preclinical findings report that female rats are more sensitive than males to the stress peptide corticotropin releasing factor (CRF) in neural circuits that mediate opioid withdrawal-induced negative affective states (Valentino *et al*, 2013). Specifically, CRF-mediated internalization of CRF type 1 receptors is less efficient in females compared with males such that females have more CRF receptors available for activation in response to stress. Although this type of mechanism could explain why women are more likely than men to use opioids to self-medicate stress and anxiety (McHugh *et al*, 2013), there are no published clinical trials testing the efficacy of CRF antagonists in female opioid addicts.

Substantial sex differences exist across all substances of abuse and in almost every facet of substance use disorders (Greenfield *et al*, 2010). Recent mandates from funding and regulatory organizations (eg, NIH and FDA) requiring researchers to consider both sexes in their studies will certainly advance our understanding of these sex differences. However, translation from preclinical to clinical research often results in an apparent attenuation of effects, as highly controlled studies in simple systems can fail to match clinical findings from complex human samples. As such, it is essential to examine not only main effects of sex on behavioral endpoints, but also potential mechanistic differences that may vary between and within the sexes. Translational approaches designed with the power to identify these complex interactions are the most likely to lead to optimal