

information in the central nervous system. In addition, this brain region sends and receives projections from the mesolimbic dopamine system so often implicated in addiction (Bannerman *et al*, 2004). Further, the hippocampus has been directly implicated in addiction behavior (Vorel *et al*, 2001), likely because of the fact that there is increasing evidence suggesting that drug addiction represents a conditioning phenomenon that is largely dependent on associations between drug effects and environmental cues (Berke and Hyman, 2000).

Coordinated hippocampal/accumbal regulation is likely at the heart of the protective addiction phenotype produced by environmental enrichment. We find that rats reared in an enriched condition (large cages with cohorts and novel objects) self-administer cocaine or amphetamine less readily than rats in the isolated control group (Green *et al*, 2009). This protective phenotype is likely mediated by a coordinated decrease in cAMP response element binding protein (CREB) activity in the accumbens coupled with an increase in the hippocampus. Further, CREB has been linked to neuronal excitability (Dong *et al*, 2006), suggesting that some yet to be identified CREB target gene may produce this protective phenotype by decreasing excitability in the accumbens and increasing excitability in the hippocampus.

Addiction-related molecular targets in the hippocampus are also being interrogated using proteomics approaches. It is known that exposure to drugs of abuse alters the expression of certain synaptic proteins. Indeed, a recent study uses this state-of-the-art technology to examine the effects of morphine administration on the protein expression profile at hippocampal synapses (Moron *et al*, 2007). This study finds that repeated morphine administration alters the synaptic distribution of endocytic proteins. This finding has functional implications, as receptor trafficking largely depends on endocytosis, and therefore morphine may alter receptor

localization by affecting synaptic redistribution of the endocytic machinery. The idea that endocytic proteins, such as clathrin, may be involved in morphine-induced changes at hippocampal synapses is quite innovative and opens up a new direction for the study of the mechanisms underlying morphine-induced neuroadaptations. In addition, these findings suggest that the study of hippocampal neuroadaptations induced by repeated morphine treatment has great potential to reveal the mechanisms contributing to the development of opiate addiction.

Addiction is a complex polygenic psychiatric condition involving many brain regions, proteins and physiological effects, not to mention varied etiologies. Understanding the molecular mechanisms underlying addictive behavior will someday allow for therapeutic intervention that will be both efficacious and safe.

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DISCLOSURE

The authors declare that except for income received from their primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional services, and there are no financial holdings that could be perceived as constituting a potential conflict of interest.

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Neuropsychopharmacology Reviews (2010) **35**, 337–338; doi:10.1038/npp.2009.106

The emerging role of integrins in neuropsychiatric disorders

Disrupted physical and functional associations between neurons are thought to govern the abnormal patterns of neural signaling that underlie neuropsychiatric disorders. As membrane signaling proteins that bridge extracellular interactions and intracellular signaling, integrins have been well studied for their role in cell migration, cell adhesion, and metastasis, but have been relatively underexplored for their contribution to mental illness and pharmacotherapy.

Integrins are obligate α - and β -heterodimers that display molecular heterogeneity, as well as developmental and regional regulation (Denda and Reichardt, 2007). Early in development, integrin signaling supports developmental events such as neuronal migration and synaptic differentiation. Integrins also contribute to the plasticity of mature synapses. In turn, both integrin expression and signaling are sensitive to drug and pathophysiological manipulation of synapses. For example, integrin subunit expression is differentially altered by acute and chronic cocaine administration (Wiggins *et al*, 2009). Such alterations are likely to be functionally important, as integrin expression can influence neuronal recovery after injury, a capacity that depends on the interaction of integrins with growth factor receptors and cytokines.

Several integrins have been associated with neuropsychiatric disorders, raising the possibility that they represent important new targets for

medication development. Recently, we provided evidence that integrins containing the β_3 -subunit (*ITGB3*) influence the serotonin system through, in part, a direct interaction with the serotonin transporter (SERT, *SLC6A4*) (Carneiro *et al*, 2008, AM Carneiro and RD Blakely, unpublished results). These findings provide a physical basis for multiple studies that have reported associations of both *ITGB3* and *SLC6A4* (and gene \times gene interactions) with autism risk. The SERT/ β_3 complex may provide an important framework for SERT regulation that likely relies on the clustering of integrins and integrin-associated proteins. Thus, targeting this complex may prove fruitful in rectifying altered serotonergic signaling in multiple neuropsychiatric disorders.

In addition, integrin- $\alpha_V\beta_3$ modulates glutamatergic signaling in the CNS. Activation of $\alpha_V\beta_3$ by ligand binding leads to selective activation of MAPK-linked signaling pathways (Watson *et al*, 2007), as well as plasma membrane trafficking of AMPA-type glutamate receptors (Cingolani *et al*, 2008). These changes alter synaptic scaling, leading to alterations in the long-term potentiation of neuronal signaling. Further studies will no doubt seek to extend these findings to determine their relationship to behaviors such as learning and memory.

Nonselective peptide ligands and novel subunit-specific ligands are used to pursue the role of integrins in neuronal function. Integrin- β_3 ligands are based on the Arg-Gly-Asp sequence present in the binding domain of extracellular matrix proteins. Cyclic Arg-Gly-Asp peptides show nanomolar $\alpha_V\beta_3$ affinities, whereas isoxazoline compounds (currently under clinical trials) show femtomolar affinities (Miller *et al*, 2000). Although these compounds were initially developed for *in vivo* mapping of malignant tumors and cancer treatment, they also provide exciting leads for reagents that can target $\alpha_V\beta_3$ -specific pathways in neurons. Furthermore, they provide a

platform for developing blood-brain barrier penetrant ligands that can probe *in vivo* contributions of integrin signaling to behavior and possibly novel treatments for devastating brain disorders.

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DISCLOSURE

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Neuropsychopharmacology Reviews (2010) **35**, 338–339; doi:10.1038/npp.2009.134

Imaging advances in developing new medications for addiction

Brain imaging has provided important insights into the clinical neurobiology of addiction for more than 20 years, beginning with the pioneering Positron Emission Tomography (PET) studies of Volkow *et al* (1988),

and continuing to recent studies showing that cocaine addiction is associated with changes in dopamine function that are predictive of choice to self-administer cocaine (Martinez *et al*, 2007). However, because of their cost and radiation hazards, PET studies of addicted subjects who are undergoing clinical trials have been limited.

Although BOLD fMRI has some disadvantages, such as lack of an absolute measure of blood flow or neuronal activity, it has the advantages of repeatability, cost, and safety over PET. One area in which fMRI has shown promise in medication development for addiction is as a predictor of treatment response in clinical trials. Recently, Brewer *et al* (2008) showed that fMRI brain activation during performance of a Stroop task in cocaine-dependent subjects before treatment was predictive of subsequent treatment response. Other studies are underway in several centers using fMRI as a baseline predictor of treatment response in clinical trials for cocaine dependence, which should provide important information about the neurobiology of medication response in addiction.

A second area that shows promise for fMRI in medication development for addictions is in the study of acute effects of medications on brain function in addicted individuals. The use of fMRI in this manner, also termed pharmacMRI or phMRI, has potential as a tool to drive medication development by providing additional information about the effects of medications before their use in costly, time-consuming phase II clinical trials (Wise and Tracey, 2006). The rationale for using phMRI in medication development for addictions is based on the following: (1) behavioral research has shown that addicted individuals show differences in behavioral performance in tasks such as cue reactivity and behavioral inhibition compared with non-addicted subjects; (2) fMRI of addicted subjects while performing these tasks has shown patterns of brain activation