[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;
[3]Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA and
[4]Departments of Pharmacology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA
E-mail: rmargoli@jhmi.edu

DISCLOSURE

Potential conflicts of interest for RLM: Consultant for AstraZeneca, grant support from Medivation, Amarin, Pfizer, and Forest Pharmaceuticals.
No conflicts of interest for CAR.

Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK (2008). The DISC locus in psychiatric illness. *Mol Psychiatry* **13**: 36–64.

Komiya Y, Habas R (2008). Wnt signal transduction pathways. *Organogen* **4**: 68–75.

Mao Y, Ge X, Frank CL, Madison JM, Koehler AN, Doud MK *et al.* (2009). Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation via modulation of GSK3beta/beta-catenin signaling. *Cell* **136**: 1017–1031.

Mei L, Xiong WC (2008). Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat Rev Neurosci* **9**: 437–452.

Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D *et al.* (2009). Common variants conferring risk of schizophrenia. *Nature* **460**: 744–7.

Wood JD, Bonath F, Kumar S, Ross CA, Cunliffe VT (2009). Disrupted-in-schizophrenia 1 and neuregulin 1 are required for the specification of oligodendrocytes and neurones in the zebrafish brain. *Hum Mol Genet* **18**: 391–404.

Neuropsychopharmacology Reviews (2010) **35**, 350–351; doi:10.1038/npp.2009.137

Antidepressants, age, and neuroprogenitors

New neurons are generated in the granule cell layer of the dentate gyrus (DG) of the hippocampus in adult humans (Eriksson *et al*, 1998). Our knowledge of adult neurogenesis in humans is quite limited and it could differ from adult neurogenesis in lower mammals. In rodents, neurogenesis is necessary for learning, and some antidepressant effects are lost in the absence of adult neurogenesis, which increases with environmental enrichment and exercise (Olson *et al*, 2006), as well as with antidepressant treatment (Couillard-Despres *et al*, 2009).

We reported (Boldrini *et al*, 2009) that selective serotonin reuptake inhibitors and tricyclic antidepressants increase dividing and neural progenitor cells (NPCs) in the DG of depressed subjects (MDD), compared with untreated MDD patients or controls. In humans, antidepressants increase the number of mitotic cells of all phenotypes in the DG, regardless of age. On the other hand, replication of NPCs, as in lower mammals, decreases with age (Couillard-Despres *et al*, 2009). This might explain why there is a poor antidepressant response in the elderly.

The functional relevance of the enhancement of neurogenesis by antidepressants needs to be ascertained by determining whether increased cell proliferation is associated with improvement of symptoms in MDD. In our study (Boldrini *et al*, 2009), a significant proportion of subjects died by suicide, which would argue against the benefits of antidepressant-induced cell proliferation, as opposed to the potential benefits of cell maturation, survival, and integration into functional neural networks, which should have a greater role in the potential beneficial impact of adult neurogenesis. Exposure to enriched environments, learning, and neurotrophins improve the survival and differentiation of newborn cells. Factors regulating cell survival and integration should be considered when examining the role of adult neurogenesis for antidepressant efficacy.

Another open question is the role of neurogenesis in the pathogenesis of MDD. Adult neurogenesis decreases with stress in rodents and is enhanced by environmental enrichment, exercise, and antidepressants. However, blunted cell replication alone does not induce depression-like behavior in mice. Growth factors, which affect neurogenesis, are decreased in MDD. Therefore, impaired hippocampal plasticity may be involved in the pathogenesis of MDD, not merely because of impaired cell replication but also because of impaired cell connectivity and functional integration into brain circuits that regulate emotional responses to the environment.

In our study, the antidepressant-induced increase in NPCs and dividing cells was associated with a larger volume of DG. Antidepressant treatment is known to increase hippocampal volume in posttraumatic stress disorder (Bossini *et al*, 2007), but no similar data are available in depression, although patients with MDD have a smaller hippocampus. The volume increase could be related to a restoration of cell number or neuropil, as antidepressants reverse dendritic shrinkage and improve cell survival, activating the antiapoptotic protein Bcl-2 and brain-derived neurotrophic factor expression in mammals.

Future studies must determine whether antidepressant response is linked to increased neurogenesis, but assessing adult neurogenesis *in vivo* is challenging. In a recent study, magnetic resonance spectroscopy was proposed as a possible method, but the specificity of the molecule used to identify NPCs was questioned and the results have not been replicated. Positron emission tomography has the limitation of low resolution and the unknown consequences of radiolabeling newborn cells. Cerebral blood volume, which correlates with angiogenesis, may prove to be a viable method for detecting neurogenesis *in vivo* (Pereira *et al*, 2007). Linking neurogenesis to improvement in depression symptomatology would justify seeking new treatments that increase not only neurogenesis but also plasticity, cell survival, and integration into functional networks.

ACKNOWLEDGEMENTS

This study was supported by PHS Grant nos MH40210, MH62185, MH64168, and MH083862, the American Foundation for Suicide Prevention, the Diane Goldberg Foundation and the Janssen Fellowship in Translational Neuroscience.

Maura Boldrini[1] and Victoria Arango[1]
[1]Department of Psychiatry, Columbia University Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, NY, USA
E-mail: va19@columbia.edu

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

Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, John MJ *et al.* (2009). Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology* e-pub ahead of print 15 July 2009).

Bossini L, Tavanti M, Lombardelli A, Calossi S, Polizzotto NR, Galli R *et al.* (2007). Changes in hippocampal volume in patients with post-traumatic stress disorder after sertraline treatment. *J Clin Psychopharmacol* **27**: 233–235.

Couillard-Despres S, Wuertinger C, Kandasamy M, Caioni M, Stadler K, Aigner R *et al.* (2009). Ageing abolishes the effects of fluoxetine on neurogenesis. *Mol Psychiatry* e-pub ahead of print 9 January 2009).

Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA *et al.* (1998). Neurogenesis in the adult human hippocampus. *Nat Med* **4**: 1313–1317.

Olson AK, Eadie BD, Ernst C, Christie BR (2006). Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus* **16**: 250–260.

Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM *et al.* (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* **104**: 5638–5643.

Neuropsychopharmacology Reviews (2010) **35,** 351–352; doi:10.1038/npp.2009.130

Normalizing drug-induced neuronal plasticity in nucleus accumbens weakens enduring drug-seeking behavior

Persistent drug-seeking behavior following long-term abstinence is a major challenge for treating cocaine or heroin addiction. Glutamatergic projections have been suggested to be a final common pathway for the initiation of drug seeking (Kalivas *et al*, 2005). In a clinical setting, neuroimaging studies have shown that cue/drug exposure increased the activity of PFC and nucleus accumbens (NAc), as well as self-reported drug craving in cocaine addicts (Goldstein and Volkow, 2002). In animal studies, a challenge of cocaine or heroin increases the synaptic release of glutamate in cocaine- or heroin-withdrawn rats as a result of the activation of corticostriatal pathways; inactivation of the corticostriatal pathway has been shown to be effective in inhibiting cocaine- or heroin-induced drug seeking (Kalivas *et al*, 2005).

Dendritic spines are the primary anatomical sites of excitatory synapses in NAc. It has been hypothesized that long-term structural plasticity in NAc contributes to certain long-lasting behaviors, including sensitization (Robinson and Kolb, 2004). Although there has been a paucity of experimental evidence that directly relates central structural plasticity to changes in specific behaviors, the density of spines on medium-sized spiny neurons in NAc is reportedly increased after repeated cocaine exposure (Robinson and Kolb, 2004; Pulipparacharuvil *et al*, 2008). By using 3D confocal image analysis of medium spiny neurons in the NAc labeled with lipophilic fluorescence dye, the spine density was found to be higher than that of spines quantified by Golgi staining (Shen *et al*, 2009). Withdrawal from cocaine injection was also reported to be associated with an increased density of larger diameter spines and reduced density of thinner spines. Moreover, a cocaine challenge after 3-week abstinence from daily cocaine treatment significantly increased the density of spines and the effect was found to be more pronounced in larger spines (Shen *et al*, 2009). These results indicate that long-lasting increases in synaptic connectivity in the NAc may provide a common ground for persistent drug seeking associated with drug addiction.

N-acetylcysteine can drive the cystine-glutamate antiporter and increase the glutamate levels after cocaine or heroin exposure. The acute or chronic administration of *N*-acetylcysteine has been shown to inhibit cocaine or heroin seeking in rats (Kalivas *et al*, 2005; Zhou and Kalivas, 2008). As well, the increase in spine head diameter induced by cocaine was also abolished in the animals pretreated with *N*-acetylcysteine. These results indicate that repeated treatment of *N*-acetylcysteine cannot only inhibit the reinstatement of drug seeking induced by cue or cocaine, but also reverse cocaine-induced neuroplasticity in dendritic spines. Importantly, the inhibition of drug seeking and normalization of spine head diameter were still present at 2 weeks after the last injection of *N*-acetylcysteine. Thus, pretreatment with *N*-acetylcysteine produces an enduring inhibition in cocaine or heroin relapse in the animal reinstatement model and normalizes changes in accumbens dendritic spines. It is hypothesized that *N*-acetylcysteine may reverse cocaine-induced neuroplasticity associated with relapse (Zhou and Kalivas, 2008). A better understanding of the normalization of the plasticity could provide guidance to develop novel therapeutic targets for treating drug addiction.

Wenhua Zhou[1,2]
[1]Laboratory of Behavioral Neuroscience, Ningbo Addiction Research and Treatment Center, School of Medicine, Ningbo University, Ningbo, P.R.China; [2]Department of Neuroscience, Medical University of South Carolina, Charleston, SC, USA
E-mail: whzhou@vip.163.com

DISCLOSURE
This work was supported by National Basic Research Program of China (2009CB522008), Nature Science Foundation of China (30670675), and United States Public Health Service Grant no. DA 015369 and NIDA INVEST Fellowship. The authors declare that, except for income received from my 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 service and there are no personal financial holding that could be perceived as constituting a potential conflict of interest.

Goldstein RA, Volkow N (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* **159**: 1642–1652.

Kalivas PW, Volkow N, Seamans J (2005). Unmanageable motivation in addiction: a pathology