

²Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;

³Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA and

⁴Departments of Pharmacology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA

E-mail: rmargoli@jhmi.edu

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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 inte-

gration 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.

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Maura Boldrini¹ and Victoria Arango¹

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

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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}

¹Laboratory of Behavioral Neuroscience, Ningbo Addiction Research and Treatment Center, School of Medicine, Ningbo University, Ningbo, P.R.China;

²Department of Neuroscience, Medical University of South Carolina, Charleston, SC, USA

E-mail: whzhou@vip.163.com

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