Neuropsychopharmacology (2010) 35, 1619–1620

www.neuropsychopharmacology.org

Commentary

SSRI-Enhanced Locus Coeruleus Activity and Adolescent Suicide: Lessons from Animal Models

Israel Liberzon*[,1,2] and Sophie A George[2]

[1]*Mental Health Service, VA Ann Arbor Health System, Ann Arbor, MI, USA;* [2]*Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA*

Neuropsychopharmacology (2010) **35,** 1619–1620; doi:10.1038/npp.2010.57

Major depressive disorder is estimated to affect 4–6% of adolescents, and selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacotherapy in children and adolescents. However, there has been concern that adolescents starting treatment are at increased risk for developing suicidal ideation and in 2004, the US Food and Drug Administration issued a 'black box' warning on SSRI prescribing to children. As a result, rates of SSRI prescribing dropped worldwide, but there was little evidence to suggest that this had a protective effect. In 2003/4 suicide rates in adolescents increased for the first time in a decade (Gibbons *et al*, 2007). However, clinical trials have limited use in detecting suicide risk as completed suicide is so rare an event that no instances of suicide and few genuine attempts are ever captured in these studies. In light of these difficulties, alternate methods for addressing this question are needed. Because many behavioral and physiological responses are preserved across species, a translational research approach may be useful in this respect.

Although suicide is a complex behavior that is extremely difficult to reproduce in animal models, it may be possible to identify proximal biological mechanisms that mediate suicidal behavior. For instance, if the biological underpinnings of impulsivity, anxiety, or depression linked to SSRI administration can be modeled in animals, and those same variables are linked to increased suicidality, animal models can point toward candidate biological mediators of increased suicidality following SSRI administration. In the following paragraphs we comment on the findings of an article published in this issue of *Neuropsychopharmacology* (West *et al*, this issue), which compares the effect of an SSRI on brain function and behavior in juvenile and adult rodents. We highlight the important contribution this study makes to the field of suicidality, depression, and antidepressant treatment.

Over the past decade an animal model that identifies activity in the locus coeruleus (LC) as a biological mediator of depression has been proposed (Weiss *et al*, 2005). It was developed following the observation that many behavioral symptoms of depression appear in conjunction with increased firing of LC neurons (Simson and Weiss, 1988). In a series of studies conducted by this group, LC activity has been convincingly linked with both aspects of depression, and antidepressant treatment, which reduces LC activity alongside reductions in depressive behaviors. Mechanistically, altered LC activity can be linked to depression and suicidality (if increased depression leads to suicidality) through changes in noradrenergic transmission, however the authors rightfully acknowledge the relationship between noradrenergic transmission and depression is not a simple one. They propose that LC firing influences mesocorticolimbic dopamine release through inhibition of dopamine neurons in the ventral tegmental area, thus linking LC activity to central reward processing and depression phenomenology.

In an exciting extension of this work, this study investigated the effect of paroxetine on LC activity, comparing the response of juvenile to adult rats. West *et al* report that adult rats treated with paroxetine always showed the expected and therapeutically relevant decrease in firing of LC neurons, but that juvenile rats did not. Younger rats treated with paroxetine sometimes showed elevated LC activity following drug administration. The authors used a swim test as an index of depressive responses to show that at the times when LC activity was high rats showed less struggling and more floating, indicating greater expression of depressive behaviors. These data provide compelling preliminary evidence that, under specific circumstances in younger rats, paroxetine can alter brain function in such a way that exacerbates depressive-like responses rather than ameliorating them.

Because the available epidemiological data suggest that a risk for suicide may be specifically related to children and adolescents, and that this risk is particularly high at the beginning of treatment, the timing and/or dose specificity of this effect is of particular interest. West *et al* report that young rats treated for longer periods showed decreases in LC activity but that firing rates were elevated in animals that had shorter treatment durations. Intriguingly, these increases only occurred after lower dose treatment.

*Correspondence: I Liberzon, Department of Psychiatry, University of Michigan, 4250 Plymouth Road, Box 5765, Ann Arbor, MI 48109-2700, USA, Tel: +1 734 764 9527, Fax: +1 734 936 7868, E-mail: liberzon@med.umich.edu
Received 25 March 2010; accepted 26 March 2010

The authors also observed that given the same amount of drug, young rats had lower paroxetine blood levels, suggesting that they may metabolize paroxetine faster. Although these observations do not fully explain the differences between the two groups (mature rats administered low doses of drug did not show elevated LC activity), together they point to a possible counterintuitive clinical strategy of increasing initial dosing levels, and/or maintaining higher blood levels with more frequent dosing as a way of reducing adverse side effects in young people.

These findings also raise additional questions that merit consideration. The model by West *et al* assumes that increases in depressive symptoms are the proximal mediator of suicidal events. Alternatively, it seems plausible that paroxetine-induced elevated LC firing represents a different proximal mechanism that serves as a mediator of increased suicide risk. Higher levels of suicidality in depressed patients are linked to comorbid anxiety (Grunhaus *et al*, 1994), and 'activation syndrome', reported in early stage SSRI treatment in some individuals (Walkup and Labellarte, 2001), is characterized by high anxiety symptoms. LC activity has been linked to anxiety and increased arousal (Berridge and Waterhouse, 2003; Bremner *et al*, 1996; but see Weiss *et al*, 1994), and desipramine, a tricyclic antidepressant that is also a potent norepinephrine reuptake inhibitor, is largely avoided in depressed patients with anxiety due to adverse clinical effects. Therefore LC activity may mediate suicidality by its effect on arousal and anxiety. The two proposed mechanisms (exacerbation of depression and enhanced anxiety) are by no means mutually exclusive and may contribute differently or additionally to increased likelihood of suicidal events.

Although the relationship between SSRIs and suicide is not yet clear, the findings presented by West *et al* provide an important step in understanding the potential link between the emergence of serious side effects and early stage SSRI treatment in young people. Further development of this and other animal models will be crucial in understanding the cellular and molecular mechanisms of depression and suicidality, and in the development of targeted treatment strategies for our patients.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

Berridge CW, Waterhouse BD (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res Rev* **42**: 33–84.

Bremner JD, Krystal JH, Southwick SM, Charney DS (1996). Noradrenergic mechanisms in stress and anxiety: I. Preclinical studies. *Synapse* **23**: 28–38.

Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA *et al* (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* **164**: 1356–1363.

Grunhaus L, Pande AC, Brown MB, Greden JF (1994). Clinical characteristics of patients with concurrent major depressive disorder and panic disorder. *Am J Psychiatry* **151**: 541–546.

Simson PE, Weiss JM (1988). Altered activity of the locus coeruleus in an animal model of depression. *Neuropsychopharmacology* **1**: 287–295.

Walkup J, Labellarte M (2001). Complications of SSRI treatment. *J Child Adolesc Psychopharmacol* **11**: 1–4.

Weiss JM, Boss-Williams KA, Moore JP, Demetrikopoulos MK, Ritchie JC, West CH (2005). Testing the hypothesis that locus coeruleus hyperactivity produces depression-related changes via galanin. *Neuropeptides* **39**: 281–287.

Weiss JM, Stout JC, Aaron MF, Quan N, Owens MJ, Butler PD *et al* (1994). Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. *Brain Res Bull* **35**: 561–572.