GIRK Channels as a Target for SSRIs

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One of the most enigmatic problems in neurobiology is the apparent disconnect between rapid effects of serotonin reuptake inhibitors (SSRI) on extracellular serotonin (5-HT) levels, and the slow onset of the therapeutic antidepressant effects of these drugs. Indeed, SSRIs increase extracellular 5-HT levels, but it is clear that subsequent neuroadaptations underlie the behavioral effects of these treatments. Identifying the adaptations associated with alleviating the symptoms of depression has been problematic at best.

One popular idea is that elevated serotonin associated with SSRI treatment down-regulates expression of 5-HT$_{1A}$ receptors that mediate autoinhibitory feedback on serotonergic terminals and cell body regions. This is quite reasonable, as numerous G protein coupled receptors have been shown to undergo desensitization-induced internalization (Claing et al. 2002). Indeed, depressed patients undergoing SSRI treatment show lower 5-HT$_{1A}$ levels than similarly depressed individuals that have not begun therapeutic treatment (Parsey et al. 2006). In rodent models there is also strong support for similar effects of prolonged SSRI exposure, but most previous investigations used biochemical assays or radioligand binding to assess changes in receptor function or expression, methods that lack cellular resolution (e.g.Blier et al. 1998; Elena Castro et al. 2003; Pejchal et al. 2002). Another important feature of these earlier studies is that they did not examine the effects of SSRI administration in animal models of depression.

In this issue, Cornellisse and colleagues report intriguing observations on the effects of SSRI treatment using cellular assays of 5-HT$_{1A}$ receptor responses in serotonergic neurons of the dorsal raphe nucleus (DRN). These studies involved electrophysiological recordings from identified serotonergic neurons in brain slices taken
from control rats, and from rats subjected to social stress, as a model of anhedonia. These socially stressed animals exhibited diminished anticipation of sucrose reward, as reported previously (Von Frijtag et al. 2000), but the authors found no evidence for reduced 5-HT₁A receptor expression in DRN. This is consistent with the notably mixed reports on the link between 5-HT₁A expression levels and depression in humans (without SSRI treatment), where some studies report enhanced receptor expression in depressed subjects (Stockmeier et al. 1998) and others report decreased expression (Arango et al. 2001).

The most exciting observation from Cornelisse et al was that only in animals chronically treated with the SSRI fluoxetine, which did indeed show a decreased 5HT₁A response, but not through receptor down-regulation. Decreased responses to either 5HT₁A or GABA<sub>B</sub> agonists were seen in DRN neurons from fluoxetine-treated animals. Both these receptor classes inhibit excitability through G proteins that activate inwardly rectifying K⁺ channels (GIRK) to hyperpolarize the membrane potential and inhibit activity (Bayliss et al. 1997; Innis and Aghajanian 1987; Innis et al. 1988; Williams et al. 1988). Both these receptor classes were inhibited in a similar manner. Perhaps surprisingly, the effects occurred in both control and socially stressed animals that were subjected to SSRI treatment, and was thus independent of the depressed state of the animals.

These findings suggest a divergence in the mechanisms underlying the etiology of depression and effective pharmacological treatment. The lack of evidence for changes in 5-HT₁A expression in anhedonic animals suggests that this receptor is not principally involved in the depressive phenotype. In contrast, treatment of depression with SSRI's
does indeed affect signaling via this receptor class by altering the expression of GIRK channels in serotonergic neurons that couple activation of 5-HT$_{1A}$ and GABA$_B$ receptors to decreases in excitability. By down-regulating GIRK rather than one specific receptor, fluoxetine parsimoniously reduces the inhibitory inputs from a number of metabotropic receptors and increases the excitability of dorsal raphe neurons, which in turn presumably increases release of serotonin, the modern panacea. Whether this study has identified novel therapeutic targets, remains to be established, but it does suggest an intriguing area for further investigation.


