GIRK Channels as a Target for SSRIs. Focus on “Reduced 5-HT₁A- and GABA_B Receptor Function in Dorsal Raphe Neurons Upon Chronic Fluoxetine Treatment of Socially Stressed Rats”

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One of the most enigmatic problems in neurobiology is the apparent disconnect between rapid effects of serotonin re-uptake 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 downregulates expression of 5-HT₁A 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-HT₁A 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 of the Journal of Neurophysiology (p. 196–204), Cornelisse and colleagues report intriguing observations on the effects of SSRI treatment using cellular assays of 5-HT₁A 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 notion that 5-HT₁A expression in humans (without SSRI treatment), where some studies report enhanced receptor expression in depressed subjects (Stockmeier et al. 1998) and others report decreased expression (Aranjo et al. 2001). The most exciting observation from Cornelisse et al. was that only animals chronically treated with the SSRI fluoxetine showed a decreased 5HT₁A response but not through receptor downregulation. Decreased responses to either 5HT₁A or GABA_B 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 SSRIs does indeed affect signaling via this receptor class by altering the expression of GIRK channels in serotonergic neurons that couple activation of 5-HT₁A and GABA_B receptors to decreases in excitability. By downregulating 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.

REFERENCES


