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SMALL RNAS

The enigma of Prozac resolved

Serotonin is a neurotransmitter associated with positive mood. Selective serotonin reuptake inhibitors (SSRIs), such as Prozac (developed by Eli Lilly; generic name fluoxetine), are used to treat depression by prolonging the action of released serotonin but often take weeks to improve symptoms. This time lag indicates that neuronal adaptations are necessary for antidepressant action. Why this occurs has remained a mystery, but a recent study published in *Science* suggests that the mechanism involves complex, reciprocal post-transcriptional regulation of serotonergic functions in the neurons of the raphe nucleus and the locus coeruleus.

The serotonin transporter (SERT) plays a part in clearance of serotonin from the synaptic cleft and is the target of SSRIs. Chronic SSRI treatment has previously been known to reduce overall SERT protein levels without affecting mRNA levels, indicating that the mechanism might involve translational control, possibly by microRNAs (miRNAs). Using *in silico* analysis, the authors identified the miRNA miR-16 as a candidate for such regulation. The raphe nucleus contains serotonergic neurons that project to the noradrenergic locus coeruleus and have been implicated in mood. The authors found that fluoxetine infusion into the raphe increased the rate of miR-16 maturation from its precursor, which was blocked by WNT3A. Overall, these data suggest that fluoxetine treatment acts directly on raphe neurons to antagonize canonical Wnt signalling and enhance miR-16 maturation, thus inducing a down-regulation of SERT and prolonging serotonergic signalling.

Under basal conditions, SERT mRNA was expressed in locus coeruleus noradrenergic neurons, but translation was inhibited by high miR-16 levels. Systemic fluoxetine in mice downregulated miR-16 levels and caused locus coeruleus neurons to acquire serotonergic functions, such as SERT and serotonin synthesis. Locus coeruleus neurons became sensitive to Prozac and represented a new source of serotonin. This surprising effect was mediated by paracrine signalling of the neurotrophic factor S100β secreted from raphe neurons. The central role of miR-16 in the action of fluoxetine was also supported by efficacy in rodent behavioural models of depression. Overall, the results suggest that the efficacy of SSRIs in treating depression depends on a decrease in SERT expression in the raphe and the *de novo* acquisition of serotonergic characteristics by noradrenergic locus coeruleus neurons, which might explain their delayed onset of action.

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ORIGINAL RESEARCH PAPER Baudry, A. *et al.* MiR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants. *Science* **329**, 1537–1541 (2010)