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NEUROLOGICAL DISORDERS

Homing in on the target of antidepressants

The mechanism of action of most commonly used antidepressants is poorly defined and a better understanding of the effects of these drugs on the brain could lead to new therapeutic approaches. A potential link between neurogenesis and antidepressant treatment announced several years ago generated excitement in the field, but the mechanisms underlying this connection have remained elusive. Now a new study by Enikolopov and colleagues narrows down the target of at least one class of antidepressants to a specific population of early progenitor cells.

Neurons are continuously generated in the dentate gyrus region of the hippocampus throughout life. In animal models, this activity increases in response to various types of antidepressant therapy, including selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, and potentially contributes to their therapeutic effects. However, the precise stage of the multi-step process of neurogenesis at which SSRIs actually intervene is unknown. A clearer understanding of the progenitor cell type targeted by these drugs could enhance understanding of the pathogenesis of depression and the development of improved antidepressants.

Quantification and characterization of different progenitor cell types by immunofluorescence is difficult, owing to the widespread, cytoplasmic expression of typical marker proteins such as nestin, combined with dense packing of the cells within the dentate gyrus. The authors therefore generated mice in which a fluorescent signal was localized specifically to the nucleus of these cells, producing a labelling pattern that was easier to quantify. In combination with staining for various proteins that are expressed at different stages of neurogenesis, the authors defined six distinct sequential stages of neuronal development and investigated the effects of chronic fluoxetine treatment on the proliferative activity of cells at each stage. Using this approach, the authors showed that the cells targeted by fluoxetine to increase neurogenesis are 'amplifying neural progenitors' — the cells generated in the second 'stage' of neurogenesis as defined in this study.

It will be vital to determine whether these cells are a common target for other types of antidepressant, and it remains to be confirmed whether these effects will translate to the human condition. Nevertheless, this study sheds light on the cells targeted by SSRIs in the brain and should direct further studies to define the precise molecular targets of these drugs. Furthermore, this model allows different early progenitor types to be more clearly defined, which could contribute to a better understanding of both hippocampal neurogenesis and the pathological effects of depression.

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ORIGINAL RESEARCH PAPER Encinas, J. M. *et al.* Fluoxetine targets early progenitor cells in the adult brain. *Proc. Natl Acad. Sci. USA* **103**, 8233–8238 (2006)

FURTHER READING Duman, R. S. *et al.* Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology* **25**, 836–844 (2001) | Santarelli, L. *et al.* Requirement of hippocampal neurogenesis for the behavioural effects of antidepressants. *Science* **301**, 805–809 (2003)