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A Small Molecule Which Protects Newborn Neurons

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Abstract

New research identifies a small molecule providing a chemical scaffold which might be useful in the design of a new class of neuroprotective drugs.

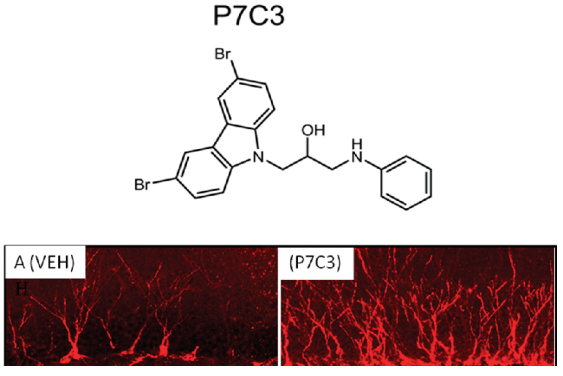
Humans and other mammals contain a pool of neuronal stem cells in the dentate gyrus of the hippocampus. As such, it is one of the few regions of the adult brain actively involved in neurogenesis, the process by which new neurons are created (*1*). The ability to regenerate neurons may also be vital in combating declines in memory and cognitive abilities due to terminal aging, Alzheimer's disease, and other neurodegenerative disorders. However, during the process of neural development, which takes weeks, many immature neurons die. Therefore, small molecules that promote neurogenesis and protect neurons during development might be useful as therapeutics. Pieper et al. have now accomplished the notable feat of uncovering a pharmacological entity endowed with these desirable neuroprotective properties (*2*).

The scientists first screened 1000 chemicals with drug-like properties for the ability to increase neurogenesis and survival of immature neurons in the dentate gyrus of the brains of living mice. Eight compounds promoted neurogenesis, of which one was quite remarkable in that it had exceptionally favorable pharmacological properties. This small molecule can be delivered orally, intravenously, or intraperitoneally. Further, it displays desirable pharmacokinetics and readily crosses the blood−brain barrier. Structure−activity relationship analyses showed that neurogenic activity of this parent small molecule can be further enhanced by substituting the hydroxyl of the chiral center of the linker with fluorine.

Having established the neurogenic activity of the small molecule, the researchers examined the mice biochemically. They found that the small molecule increases the survival rate of neural precursor cells by protecting mitochondrial membranes supporting an antiapoptotic mode of action.

The researchers then tested the small molecule in two cases where there are deficits in neurogenesis. First, in adult knockout mice which have an obvious defect in neurogenesis, the small molecule enhances hippocampal neurogenesis. Second, in addition to enhancing neurogenesis in aging rats, it successfully abates cognitive decline and prevents age-related weight loss.

This is a truly landmark study. In modern times, high-throughput screening methods coupled to *in vitro* assays have become increasingly popular in identifying promising compounds. High-throughput screening of compounds in small whole-animal model organisms such as worms, flies, and zebrafish have also gained momentum. What is perhaps most remarkable about the current study is that a relatively straightforward screening process in a mammalian system has successfully yielded a chemical entity with immense potential. Future studies will shed light on the precise details of the mode of neuroprotection, but already this small molecule provides a chemical scaffold for the design of a new class of promising therapeutics.



Increased neurogenesis upon administration of small molecule P7C3 compared to vehicle alone. Image courtesy of A.A. Pieper and S.L. McKnight. Reprinted with permission from Elsevier, Inc., ref *2*.

References

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