Turning down, but not off

Neuroprotection requires a paradigm shift in drug development.

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The industrialized world faces an unusual predicament. The demographic shift towards an ageing population, coupled with the prevalence of Alzheimer's disease and vascular dementia (both of which cause cognitive decline), has led economists to estimate that by 2050, the entire economy of the industrialized world could be consumed by the costs of caring for the sick and elderly. What can be done to abate these dreaded neurodegenerative diseases and their socioeconomic effects?

Until recently, only symptomatic approaches were available — for example, cholinergic drugs for Alzheimer's disease, which mildly enhance memory by increasing levels of the neurotransmitter acetylcholine. But the concept of 'brain protection' raises hope that neurons can be preserved from the ravages of neurodegenerative insults.

In most neurodegenerative diseases, the brain is attacked and nerve cells are killed by a variety of overactive signalling pathways. These pathways are triggered by conditions such as oxidative or nitrosative stress, accumulation of aberrant proteins, and excessive activity in the brain of the neurotransmitter glutamate (excitotoxicity). Excitotoxic damage, a common final pathway contributing to most or all neurodegenerative disorders, is largely caused by overstimulation of NMDA-type glutamate receptors. This causes excessive influx of Ca^{2+} through the receptors' associated ion channels, resulting in detrimental enzymatic reactions and generation of toxic oxygen and nitrogen free radicals.

These neurodegenerative processes could be potential drug targets for neuroprotection. For example, injurious agents or instigators of degeneration could be counteracted, as in the case of excessive amounts of glutamate, which excite neurons to death, or aberrant proteins (such as mutant parkin protein in juvenile Parkinson's disease) that clog the brain's detoxification and degradation systems. Other examples include the depression of 'death' signalling pathways by inhibiting enzymes such as caspases; restoration of pathways that degrade aberrant proteins through the proteosomal and lysosomal systems; or enhancement of survival pathways, with either anti-cell-death proteins or neurotrophic factors that prolong neuronal life. Cell-based approaches could also be advanced with attempts to ameliorate inflammatory cell activities, and stem-cell replacement therapy to provide new brain cells.

But there is a paradox. Many of these potential targets have normal functions,

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which only become deleterious to the nervous system when in excess or under maladaptive conditions. For example, physiological NMDA-type glutamate receptor activity is essential for normal neuronal development, communication between neurons and memory formation. Neuroprotective agents that work by high-affinity binding to these receptors block all activity, and these drugs produce unacceptable side effects including hallucinations, drowsiness and coma. Similarly, microglia and astrocytes nurture and protect the neurons they surround, and only release toxic substances when they are inappropriately perturbed. We cannot simply shut off these cell processes and molecules without compromising normal or adaptive functions.

What is needed is a way to target neuroprotective drugs and cell-based therapies at abnormal functions in an appropriate spatial and temporal pattern for the disease, while sparing normal, physiological activity. But drug discovery in the big pharmaceutical companies involves high-affinity screening of target molecules — hence these drugs work 'too well' and 'all the time'. If we use an analogy of the target molecule as a television set, these 'competitive' drugs battle one-on-one with the agonist at the on/off switch (the agonist binding site) and, when successful, will simply turn the set off. A neuroprotective agent that works by high-affinity binding to the receptor of a neurotransmitter will block all activity — normal and abnormal. In addition, such drugs will outcompete lower (physiological) levels of neurotransmitter more effectively than higher (pathological) levels, meaning that normal areas of the brain will be shut off even before pathological areas are effectively protected. Thus, such drugs manifest unacceptable side effects by blocking normal physiological activity in all parts of the brain, even those not affected by the disease process.

What if the brain could be protected using drugs that do not bind very well under physiological conditions, but that under pathological conditions become selective for the target? Using the television analogy, such a drug would be equivalent to the volume control. For example, excitotoxicity could be prevented by turning down the excessive 'volume' of Ca^{2+} influx through the receptor's channel towards normal, thus avoiding the formation of free radicals. But if the drug binds with high affinity in the channel, it will accumulate there, and once again block normal function — turning the volume all the way down is as bad as turning off the on/off switch.

On the other hand, a clinically tolerated drug would block only excessive activity while relatively sparing normal function, simply by adjusting the volume towards normal levels. Such drugs are termed uncompetitive inhibitors — they work better when increasing levels of agonist are present, hence blocking excessive (pathological) receptor activity while sparing lower (physiological) activity. A key to this mechanism is not only drug selectivity for the target despite low affinity but, most importantly, the ability to come off the target relatively quickly, preventing accumulation and blocking of subsequent normal function. One such drug is memantine, which my colleagues and I discovered can preferentially block NMDA-glutamate receptor-associated ion channels when they are excessively open. Memantine has recently been approved for treatment of Alzheimer's disease in Europe and the United States.

By virtue of their relatively gentle binding, drugs of this type work best under pathological conditions, while exerting minimal effects on normal brain activity. This simple concept could be extended to other neuroprotective targets — even to other pharmaceuticals — and in my opinion will be significant in future drug design. ■

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FURTHER READING

Chen, H.-S. V. *et al. J. Neurosci.* **12,** 4427–4436 (1992).
Lipton, S. A. & Chen, H.-S. V. *Cell Death Diff.* **11,** 18–20 (2004).
Lipton, S. A. & Rosenberg, P. A. *N. Engl. J. Med.* **330,** 613–622 (1994).
Reisberg, B. *et al. N. Engl. J. Med.* **348,** 1333–1341 (2003).