WEB WATCH

Your history

- http://faculty.washington.edu/chudler/hist.html

What are the most important events in the history of neuroscience? Opinions will vary, but a good place to arm yourself with some of the relevant knowledge is Eric Chudler's 'Milestones in Neuroscience Research'. The bulk of the site comprises a straightforward chronological list of key events in the history of neuroscience, with links to biographies of many of the main thinkers that have shaped the field.

According to Chudler, the history of neuroscience can be traced right back to 4000 BC, when the euphoriant effect of the poppy plant was first recorded. However, it was not until around 2,000 years later that the legendary Edwin Smith Surgical Papyrus — thought to be the earliest written record of the nervous system (and to include the first documented use of the word 'brain') — was produced. It is also interesting to read that the great philosopher Aristotle was convinced that the heart was the seat of human intelligence, even though the likes of Plato and Hippocrates were already on the right track many years earlier.

As Chudler readily admits, this is by no means an exhaustive list, and there are some notable omissions. For example, developmental neuroscience is hardly covered at all — not even Spemann and Mangold's seminal work on neural induction gets a mention. Nevertheless, the site is informative, and it includes links to sites on a diverse range of neuroscience-related subjects, including the history of phrenology, and a chronology of psychoactive substance use.

After all that, anyone seeking some light relief (and a little subliminal learning, perhaps) might like to try out the word-search puzzles that feature the names of key neuroscientists through the ages!

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AXON GUIDANCE

Local government

Although it is becoming widely accepted that protein synthesis takes place in dendrites, the idea that axons might use proteins made in the growth cone for growth and guidance is still controversial. This is rather surprising, because it has been known for many years that growth cones contain ribosomes, so the idea of local protein synthesis is not particularly far-fetched. However, it is only recently that we have begun to explore this possibility, and as Campbell and Holt now report in *Neuron*, some fascinating discoveries have already come to light.

Using *Xenopus* retinal ganglion cells (RGCs) in culture, the authors tested the response of growth cones to three molecular cues: semaphorin 3A (Sema3A), netrin 1 and L-α-lysophosphatidic acid (LPA). Sema3A and LPA both induce RGC growth cones to collapse, and Sema3A can also cause repulsion. The response to netrin 1 depends on the culture conditions — on fibronectin, RGC growth cones are attracted to netrin 1, but on laminin they are repelled.

The authors went on to show that if RGCs were treated with translation inhibitors, such as anisomysin or cycloheximide, their growth cones no longer collapsed or turned in response to Sema3A or netrin 1. Importantly, this treatment did not affect the forward extension of the growth cone, indicating that it is growth cone steering, rather than advancement, that depends on protein synthesis. The collapse response to LPA was unaffected by translation inhibitors, but interestingly, it was abolished if proteasome-dependent protein degradation was blocked, as were the attractive and repulsive responses to netrin 1. Together, these observations indicate that protein synthesis and degradation are both important for different aspects of axon guidance. The chemotropic response to Sema3A seems to depend only on protein synthesis, whereas the response to LPA requires protein degradation. The response to netrin 1 seems to be more complex, in that it requires both protein synthesis and degradation.

However, these data still do not tell us whether protein levels are being controlled locally in the growth cone or centrally in the cell body. To address this issue, Campbell and Holt carried out the same experiments, but using growth cones that had been isolated from the cell body. Intriguingly, they found that detachment from the cell body did not prevent any of the chemotropic responses. They also showed that all of the molecular apparatus for protein synthesis and proteasome-dependent degradation are present in the growth cone, and that these pathways can be activated locally by guidance cues — netrin 1 and Sema3A activate the eukaryotic translation initiation factor eIF-4E, and netrin 1 and LPA cause certain proteins to become conjugated to ubiquitin, thereby priming them for degradation.

The idea of local protein synthesis and degradation at the growth cone is undoubtedly appealing, as it would neatly explain how growth cones can react so quickly to a constantly changing environment as they travel to their targets, even though their cell body might be a considerable distance away. Campbell and Holt's work opens up a whole new area of investigation into axon guidance, and it is hoped that future studies will identify the proteins that are synthesized and broken down in response to guidance cues, and show how these changes are translated into a chemotropic response.

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References and links

ORIGINAL RESEARCH PAPER Campbell, D. S. & Holt, C. E. Chemotropic responses of retinal growth cones mediated by rapid local protein synthesis and degradation. *Neuron* **32**, 1013–1026 (2001)

FURTHER READING Mann, F. & Holt, C. E. Control of retinal growth and axon divergence at the chiasm: lessons from *Xenopus*. *Bioessays* **23**, 319–326 (2001) | Job, C. & Eberwine, J. Localization and translation of mRNA in dendrites and axons. *Nature Rev. Neurosci.* **2**, 889–898 (2001)

WEB SITES

Encyclopedia of Life Sciences: http://www.els.net/ axon guidance | visual system development in vertebrates