International Society for Neuroethology

Newsletter - July 1997

NEUROETHOLOGICAL VIEWPOINTS

With this issue of the Newsletter we introduce Neuroethological Viewpoints. These articles, as in the following piece by David King, provide thoughtful ideas on a particular issue that should be of interest to a large number of neuroethologists. See the article about changes in the Newsletter for submission information.

IS THERE A ROLE FOR COMPARATIVE GENETICS IN NEUROETHOLOGY?

Flies comprise a wonderfully diverse group for neuroethology, exhibiting some extraordinary behavioral differences. Some years ago I began a survey of axonal size distributions in the cervical connectives of various fly species. On the basis of previous experience, I expected to find identifiable individual neurons with similar characteristics in related species. But I was astonished by the wide variation in axonal diameter that appeared in different flies. (Details remain unpublished, although they have been presented at several meetings; e.g., King 1988.) These observations suggested, perhaps unsurprisingly, that evolution had exerted exquisite control over the shape of many individually identifiable neurons. John Edwards once quipped that my slides of flies' necks displayed coded "ideograms" of each species' behavior, with the sizes of various axons representing the adaptive importance of particular pathways.

Neuronal function depends on numerous anatomical and physiological parameters, including axon diameter. Since a limited genome could not possibly permit so many variables to be "concatenated without limitations" (Bullock 1976), I began to wonder whether any simplifying generalizations might arise from an evolutionary perspective.

Perhaps some general rules govern the translation of genetic mutations into changes in neuronal organization. How could gradual evolution, based on specific mutations within a limited set of genes and proceding in small steps from an ancestral state, yield such diverse adaptive design at the level of individually identifiable neurons?

If only genes had "tuning knobs" for manipulating the parameters most critical for neuronal function! Finding those knobs could then tell us what neuronal features were adaptively important. The idea of a tuning knob offers a familiar metaphor for a modular mechanism that enables graded and reversible adjustment of a parameter. A small set of tuning knobs can permit a gradual approach toward any one of a vast array of possible configurations, just as a few knobs on a microscope can be used to frame and focus images of any region, large or small, anywhere on a specimen.

At the time, I had never heard of adjustable genes. Nevertheless, consideration of how useful adjustable neuronal parameters could be led me to imagine a way to make tuning knobs from repetitive DNA. Repetitive DNA experiences frequent, small and reversible alterations in repeat number. If the number of repeats could somehow affect the regulation of some genetic trait, then spontaneous mutations could "twiddle the knob", providing genetic variation for efficient evolutionary transformation from one parameter state to another. For several years this scenario

seemed wildly speculative. There was scant evidence (none of it known to me) that repetitive DNA did anything at all, let alone regulate genetic traits as a function of repeat number.

Then came the discovery that several human neurological disorders are caused by excessive expansion of repeated CAG triplets, a phenomenon which was widely reported as "unexpected" and "puzzling". Remarkably, disease severity and latency to onset are linked to the number of repeats. I couldn't overlook the parallel between these mutation-prone, disease-causing genes and my hypothetical "tuning knobs". I proposed (King 1994) that such odd DNA sequences might function normally as quantitative gene regulators with an advantageous evolutionary role. By now there is clear evidence that CAG triplets, as well as microsatellite sequences with other motifs, do indeed occur within many normal regulatory genes where they can influence gene transcription activity. Such repetitive sequences appear to equip the genome with adjustable "tuning knobs" that can facilitate evolution (King *et al*. 1997).

Following separate paths, both comparative neurobiology and clinical neurology have led to a novel mechanism that permits small, reversible mutations in regulatory genes. I would invite ISN colleagues to consider the following hypothesis. Regulatory genes that contain microsatellite sequences may help implement evolutionary flexibility. When expressed in nervous tissue, such loci may indicate genetically variable parameters that have neuroethological significance. Conversely, behavioral differences among related species may point to the existence of adjustable genes for regulating relevant parameters of neural organization. Excessive expansion of certain triplet repeats may cause neurological disease, but normal variation at the same loci may have been an important source of variability during the evolution of the human nervous system.

References

King DG 1988 On the evolution of specialized neuronal form: Phylogenetic variation in cervical giant axons of flies (Diptera). *Proc. XVIII Int. Congress of Entomology*, p. 70.

Bullock TH 1976 In search of principles in neural integration. In: *Simpler Networks and Behavior*, John C. Fentress, editor. Sinauer Associates, Inc., Sunderland, Massachusetts.

King DG 1994 Triplet repeat DNA as a highly mutable regulatory mechanism. *Science* 263:595-596.

King DG, Soller M, and Kashi Y 1997 Evolutionary Tuning Knobs. *Endeavour* 21:36-40.

David G. King, E-mail: dgking@siu.edu