

ness to *M. leprae* in lepromatous patients. The report by Haregewoin *et al.* would suggest that organisms which are cross-reactive with *M. leprae* but have unique determinants capable of triggering T cells to secrete IL-2 or other appropriate lymphokines might be able to initiate the expansion of T-lymphocyte clones capable of mediating cell-mediated immunity and activating macrophages to kill and degrade *M. leprae*. These results may provide an important insight into a general mechanism for overcoming immunological unresponsiveness or suppression, with ramifications far beyond leprosy.

Beyond the scientific results presented, a further aspect of this work is worthy of note. The research of Haregewoin *et al.* was sup-

ported by the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases, and the senior author is a recipient of a training fellowship from WHO. The work represents a collaboration between laboratories in Addis Ababa, Ethiopia and Oslo, Norway. This kind of linkage should serve as a model for accelerating access by researchers in developing countries to conceptual and technical advances in basic sciences to enable them to contribute more effectively to the solution of problems of both fundamental and practical importance. □

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Neuropeptides

Complex proteins coordinate simple behaviour

from Charles F. Stevens

THE small family of neuropeptides that controls the egg-laying behaviour of the marine snail *Aplysia*^{1,2} provides a striking example of a general trend in biological sciences: over the past decade, biological systems have come to seem more complex and less economical than we had thought. Traditional notions of their elegance and parsimony have been challenged on several fronts. For example, new findings about the structure of the genome — which has become incredibly tacky by old standards — and the daunting array of ionic channels responsible for the electrical activity of the nervous system, seem to demand new organizational principles. The synthesis and function of neuropeptides, as illustrated by the recent work of Richard Scheller, James Jackson and their collaborators at Columbia University, offers another such challenge; but in this case the organizational principle is not far to seek.

Egg-laying behaviour in *Aplysia* is initiated by a group of associated neurones called the bag cells. When these cells become active, the animal extrudes a string of eggs which it then arranges in a mass and attaches to the substrate with its mouth. The entire sequence of behaviour is known to be controlled by a related group of polypeptides, one of which is the egg-laying hormone (ELH).

ELH is the principal protein product of the bag cells, and the Columbia group began their analysis of the neuropeptides controlling egg-laying behaviour by cloning cDNA that codes for ELH. They were then in a position to use this cDNA as a probe to identify other related genes.

By this strategy, they uncovered a family of at least nine closely related genes involved in the control of egg laying.

Although the work of the Columbia group has many interesting facets, two im-

portant generalizations stand out. First, the neuropeptides are synthesized as part of a larger polypeptide and produced from it by proteolytic processing. Second, the overall behaviour is governed by products of a gene family, of which different members are expressed by different cell types. Thus, components of the egg-laying system that are functionally related clearly have a common evolutionary origin, revealed in the strong homologies between genes that define the family.

Scheller *et al.*² have now sequenced three representatives of this family. The genes code for products that share properties with polypeptides from other systems³: the polypeptide has a signal sequence characteristic of secreted proteins, and contains multiple functional peptides delimited by amino acid sequences recognized by trypsin-like proteases. Thus, on proteolysis, the polypeptide can give rise to multiple neuropeptides. The ELH gene expressed by bag cells contains sequences for ELH itself as well as three or four other small peptides thought to be involved in controlling the snail's behaviour.

The ELH polypeptide contains ten potential cleavage sites (pairs of basic amino acid residues) which, if they were used in all possible combinations, could produce 1,024 distinct polypeptides. Presumably most of these potential products are not made, but this calculation vividly illustrates how polypeptides such as the ELH precursor may produce a diversity of peptides from a single gene. These multiple products from a single gene may function, at least in part, to coordinate components of a complex system. ELH itself will mediate some, but not all aspects of egg-laying behaviour, and additional factors encoded by the ELH gene are necessary for the entire set of behaviours.

Two other representatives of this gene family are responsible for initiating egg-laying behaviour. They code for products known as the A and B peptides, and are about 90 per cent homologous with the ELH gene. The A and B peptides are expressed by cells in the atrial gland, a secretory organ associated with the reproductive tract, and initiate egg-laying behaviour by causing bag cell discharge. The discharge is produced in an interesting way. Binding of the appropriate ligand to bag cell receptors activates an adenylate cyclase which, through the production of cyclic AMP, ultimately causes bag cell channel properties to be modified so that a sustained discharge results. The bag cell discharge induces the release of ELH and its related peptides, and these neuropeptides in turn elicit the appropriate further changes in the nervous system that give rise to egg-laying behaviour. The evolutionary link between the ELH gene and the A and B peptide genes thus has a functional parallel in that different cells expressing the various members of the gene family all serve the final goal of eliciting a single complex behaviour pattern.

The Columbia group is now in a position to follow three important lines of research on the control of behaviour by neuropeptides. Cells expressing genes belonging to this family can be found by hybridization *in situ*. This method exploits homologies between members of a family by using a labelled cDNA of one member as a probe to detect mRNA copied from related genes in other cells. Insofar as evolutionary relationships between genes imply functional relationships between their products, the method can be used to uncover the network of neurones that subserve components of the egg-laying behaviour. Second, because expression of genes in this family must be developmentally regulated, the cDNA probes can be used to discover the sequence in which these genes are expressed and the relationships between them. Finally, cells such as the bag cells, expressing members of this gene family, can be used to investigate the processing of polypeptide precursors that result in the diversity of products and the coordinated release of multiple products.

Neuropeptide control of egg-laying behaviour involves a rather large variety of peptides and is, according to older concepts, rather complex. The molecular biological approach to this problem, however, seems to be revealing an underlying order and may explain why small peptides should be manufactured as parts of a polypeptide. Perhaps we are starting to perceive a new simplicity in the relationship between brain function and behaviour. □

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2. Scheller, R.H. *et al.* *Cell* 32, 7 (1983).
3. Herbert, E. & Uhler, M. *Cell* 30, 1 (1982).