Neurobiology

Social eating for stress

Marla B. Sokolowski

One type of the nematode worm *Caenorhabditis elegans* feeds alone, another in aggregates. The neurobiological underpinnings of these behaviours are now being revealed at the molecular level.

Behavioural ecologists have shown that many animals form social groups in response to stressful environmental conditions. Neurobiological evidence for this behaviour has now been discovered in the nematode worm, *Caenorhabditis elegans*. On pages 899 and 925 of this issue, de Bono *et al.*[1] and Coates and de Bono[2] present striking results on the genetic, molecular and neural mechanisms underlying nematode social feeding. These discoveries provide tantalizing insights into the effects of stress in social groupings.

Caenorhabditis elegans has a fixed quota of 302 neurons, and with the availability of modern genetic and molecular tools it has become a superb model for studying behavioural neurobiology. Many of its neurons are being traced to specific functions that link genes and behaviour through neural circuitry[3]. As far as the *C. elegans* response to food is concerned, there are two naturally occurring foraging behaviours[4]: individuals of one type feed alone (solitary) whereas the other type feeds in aggregates ('social'; the term is used loosely because it is not yet clear that this is true social behaviour). The two variants are known to arise from a single amino-acid difference in a putative neuropeptide receptor protein (NPR-1), which is related to the mammalian neuropeptide Y receptor family. Solitary feeders show reduced locomotion and high dispersal activity when encountering food (a 'lawn' of bacteria); social feeders, by contrast, continue to move rapidly towards food and eventually aggregate on the borders of the lawn.

De Bono and colleagues screened mutant strains of *C. elegans* for mutations affecting social feeding, and found several that interacted with the *npr-1* gene. Using green fluorescent protein as a marker (Fig. 1), they then looked at where the genes concerned are expressed, and identified the relevant neurons. They also targeted the expression of each gene to subsets of the neurons, to determine where each gene is required. To confirm that these neurons are indeed involved in the animals' social behaviour, they ablated each neuronal cell using a laser or blocked its electrical activity. This combination of approaches allowed the authors to identify two sets of neurons. One set is found in the animal's anterior, and is likely to be responsible for sensing the external environment[1]. The other occurs in tissues bordering the structure containing the body fluids. Presumably, cross-talk between the two systems controls the nematodes' solitary or social response to food.

In the first paper, de Bono *et al.*[1] show that social feeding is induced in a crowded feeding environment, after perception of this condition by the anterior neurons known as ASH and ADL. ASH neurons sense both mechanical and chemical stimuli, whereas ADL neurons are involved in odour avoidance. But more notably, these neurons are both nociceptive — they detect pain or aversive conditions such as crowding or food shortage. Ablating either ASH or ADL neurons prevents aggregation in response to crowding. On this evidence, then, social feeding in *C. elegans* may be a response to stressful conditions.

Solitary feeders aggregate when the *npr-1* gene is deleted, suggesting that *npr-1* represses social feeding. *npr-1* is primarily expressed in the nervous system and is not required during development for repression of social feeding[2]. Mutations in other genes, *osm-9* and *ocr-2*, restore solitary feeding behaviour in *npr-1* mutant animals[1]. These genes are predicted to encode components — subunits of a membrane cation channel called TRPV — that are thought to form a sensory transduction channel in several *C. elegans* sensory neurons. The subunits of TRPV are required in either ASH or ADL neurons, both of which are involved in detecting aversive stimuli to trigger social feeding. Interestingly, *C. elegans osm-9* and *ocr-2* are respectively related to genes encoding the mammalian vanilloid (capsaicin) receptor TRPV1(VR1), which is implicated in sensing thermal pain, and the TRPV4 channel, which responds to mechanical and osmotic stimuli.

In the second paper[2], Coates and de Bono implicate a different ion channel, in a different place, in regulating social feeding. This channel is controlled by the signalling molecule cyclic GMP, and is composed of the subunits TAX-2 and TAX-4. The data[2] again support the idea that NPR-1 inhibits social feeding, and that here TAX-2 and TAX-4 regulate responses to signals that promote aggregation by sending antagonistic signals via the body fluid. From an evolutionary perspective, this pathway might have arisen to regulate the relative numbers of solitary and social animals, as each strategy would have associated costs and benefits depending on the environment. Given that neuropeptide Y is involved in regulating food intake in mammals, an intriguing question here is whether *npr-1* differentially affects the food intake of solitary and social-feeding *C. elegans*, and if so what the consequences are on the animals' fitness.

Each paper presents a model to explain how social feeding is regulated, with one system sensing the external environment and the other involving neurons inside the body cavity. But in neither paper is the attempt made to connect the two. It remains unclear how these molecular and neural

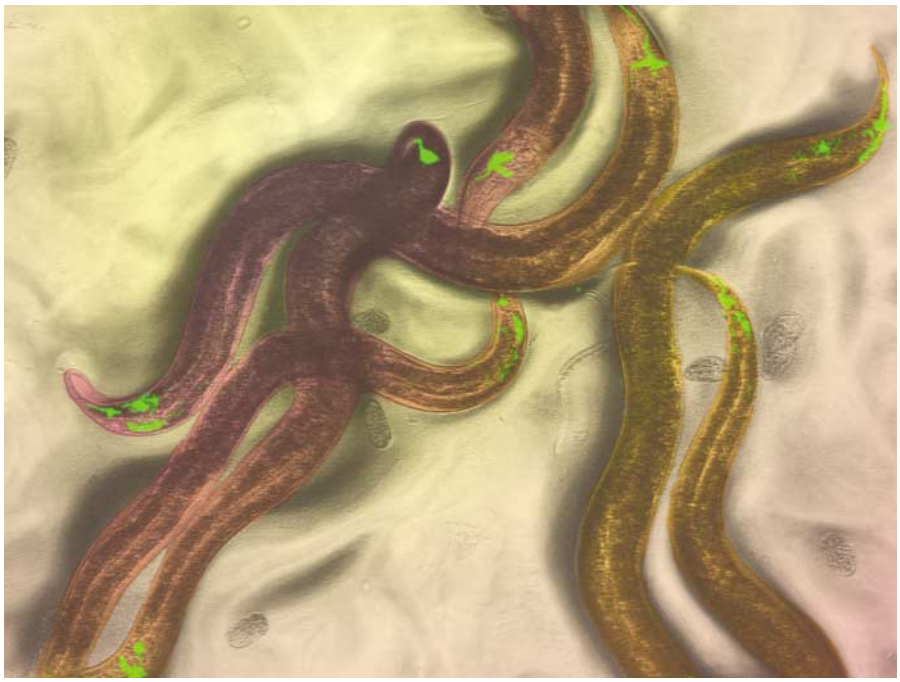

Figure 1 **Glow worms — social *C. elegans* displaying expression of green fluorescent protein. (Image courtesy of S. Reichelt and M. de Bono, LMB, Cambridge.)**

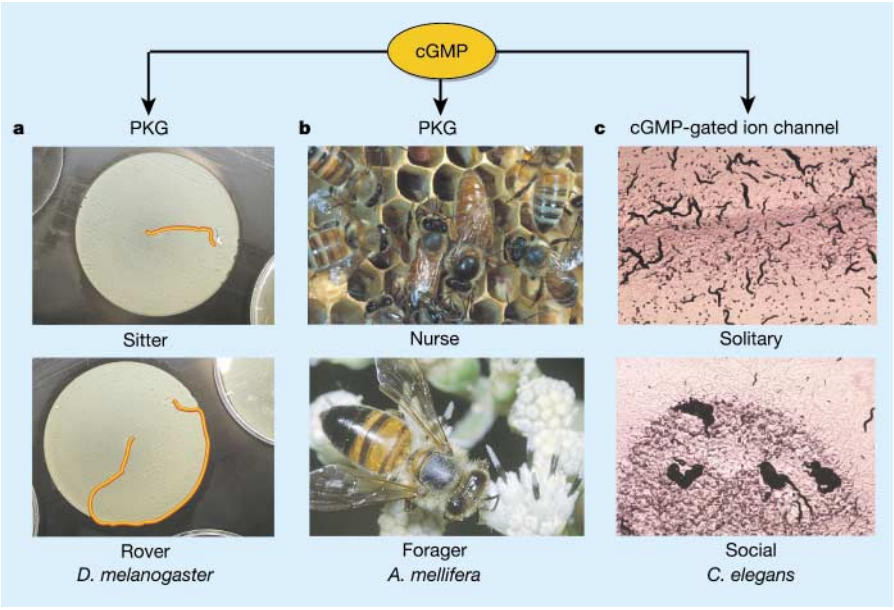

Figure 2 **The cyclic-GMP signalling pathway and variation in food-related behaviours.** a, **In the fruitfly *Drosophila melanogaster*, two different food-search behaviours — the self-explanatory 'sitter' and 'rover' — depend on variants of the *foraging* (*for*) gene, which encodes a cGMP-dependent protein kinase (PKG)[5]. Shown here are 5-minute foraging trails of fly larvae.** b, **In the honeybee *Apis mellifera*, *for*, and so PKG, is upregulated when bees switch from nursing in the hive to foraging for nectar and pollen[6].** c, **Aggregation in *Caenorhabditis elegans* involves a cGMP-gated ion channel, as shown by Coates and de Bono[2]. Adverse conditions such as crowding or food shortage affect food-related behaviours in all of these organisms.**

mechanisms act in the animal as a whole to regulate social behaviour.

How about the situation in other organisms? Signalling through cGMP is also associated with normal variation in food-related behaviour in the fruitfly *Drosophila melanogaster* and the honeybee *Apis mellifera* (Fig. 2). In two cases, variation in behaviour is determined as natural variation in a single gene — *npr-1* in the nematode, and *foraging* (*for*) in the fruitfly. The *for* gene encodes a mediator of cGMP action, a protein kinase enzyme known as PKG. As their names suggest, flies with the *for* variants *rover* or *sitter* differ in their locomotory behaviour on food, and in PKG levels[5]. In honeybees, the effect occurs through gene regulation rather than variation: when bees shift from working in the hive to foraging, *for* is upregulated[6]. Levels of PKG thus affect food-related behaviours over different timescales — over evolutionary time in *Drosophila* and over the lifetime of the individual honeybee.

So, has natural selection acted on different signalling molecules (the cGMP-gated ion channel in *C. elegans*, and PKG in flies and bees) in the same pathway to modulate food-related behaviours in these three species[7]? An obvious experiment is to determine whether *npr-1* and *for* lie in the same cGMP signalling pathway, and if they do whether there are similarities in the neural substrates involved. Whether cGMP signalling is involved in mammalian food-related behaviours also remains to be seen.

The discovery of an association between social behaviour and neurons that respond to aversive conditions is exciting because it provides a mechanistic basis for observations from behavioural ecology. A common theme in this rich literature is that adverse environmental conditions stimulate the formation of groups[8]. For example, solitary locusts become gregarious in response to drought, and birds of some species postpone mating to help their parents in the nest when new nest sites are scarce.

Many questions remain, of course. Is there a common neurobiological theme to group formation in response to stressful ecological conditions? Is the formation of social groups in general associated with neurons that sense aversive stimuli? Finally, if sociality has indeed evolved in response to stress, have the neurobiological underpinnings in simple organisms such as *C. elegans* provided the evolutionary basis for more complex social behaviours? ■

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100 YEARS AGO

The Huxley Memorial Tablet… was unveiled at the Ealing Public Library on Thursday last by the Mayor of Ealing, Alderman H. C. Green. The inscription on the tablet is, "The Right Honourable Thomas Henry Huxley. Born at Ealing, 4th May, 1825. Died at Eastbourne, 29th June, 1895. Try to learn something about everything, and everything about something."

ALSO…

The third annual Huxley memorial lecture was delivered at the Anthropological Institute on October 21 by Prof. D. J. Cunningham, F.R.S. The subject was "Right-handedness and Left-brainedness," and Prof. Cunningham referred to the general interest which it presents to all students of anthropology. So far as available evidence goes, it seems probable that right-handedness was a characteristic of man at a very early period in his evolution… Investigation shows that right-handedness is due to a transmitted functional pre-eminence of the left brain… The greater part, if not the whole, of the motor incitations which lead to articulate speech go out from the speech centre which resides in the left cerebral hemisphere. In left-handed people, the predominance of the right cerebral hemisphere is accentuated by the transference to it of the active speech centre. Left-handed people, therefore, speak from the right brain.
From *Nature* 30 October 1902.

50 YEARS AGO

The practice at the Royal Observatory, Greenwich, of dropping the Time Ball, the symbol of Greenwich time throughout the world, was resumed at 1 p.m. on October 26. The Time Ball is a dull red sphere, 5 ft. in diameter; it is part of the Wren Observatory building and was erected for the purpose of enabling masters of vessels proceeding down the Thames to adjust their chronometers. The Time Ball is raised half-way up a mast, on which it slides, at five minutes to one, hauled to the top at two minutes to one, and released electrically on the hour. It was the earliest means of making Greenwich mean time known to the public, but the system has now been superseded for all practical purposes by the six pips broadcast by the B.B.C. and by the speaking clock operated by the G.P.O. The Ball was operated continuously from 1833, when first installed, until the Observatory was evacuated during the Second World War.
From *Nature* 1 November 1952.