had already accumulated in North Atlantic strata and then, through the consequent environmental changes, carbon from other sources such as methane from widely dispersed gas hydrates.

A better understanding of the relationship between the sills, conduits and carbon-cycle perturbation at the IETM will require more work. But if that relationship is one of cause and effect, the significance of the IETM escalates dramatically. In the hydrate-dissociation scenario[3,6], deep-ocean warming drove the massive release of carbon, making events at the IETM an intriguing but imperfect analogue of current fossil-fuel emissions. The volcanic triggering of methane release from the sea floor, whether that methane was biogenic or thermogenic, instead implies that sudden hydrocarbon input caused extreme warming, a view consistent with analyses[2] of temperatures at the IETM. Given the comparable estimates for carbon release at the IETM (1,500 to 3,000 Gt)[3,4], and anthropogenic release of carbon into the atmosphere over the coming centuries (3,000–4,000 Gt), environmental change during the IETM should become the subject of general investigation. ■

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1. Kennett, J. P. & Stott, L. D. *Nature* **353,** 225–229 (1991).
2. Zachos, J. C. *et al. Science* **302,** 1551–1554 (2003).
3. Dickens, G. R., O'Neil, J. R., Rea, D. K. & Owen, R. M. *Paleoceanography* **10,** 965–971 (1995).
4. Svensen, H. *et al. Nature* **429,** 542–545 (2004).
5. Bralower, T. J. *et al. Geology* **25,** 963–966 (1997).
6. Katz, M. E., Pak, D. K., Dickens, G. R. & Miller, K. G. *Science* **286,** 1531–1533 (1999).
7. Farley, K. A. & Eltgroth, S. F. *Earth Planet. Sci. Lett.* **208,** 135–148 (2003).
8. Shipboard Scientific Party. *ODP Prelim. Rep. 107* www-odp.tamu.edu/publications/prelim/207_prel/207PREL.PDF (2003).
9. Dickens, G. R. *Bull. Soc. Geol. Fr.* **171,** 37–49 (2000).
10. Kvenvolden, K. A. *Chem. Geol.* **71,** 41–51 (1988).
11. Kent, D. V. *et al. Earth Planet. Sci. Lett.* **211,** 13–26 (2003).
12. Kurtz, A. C., Kump, L. R., Arthur, M. A., Zachos, J. C. & Paytan, A. *Paleoceanography* **18,** 1090 (2003).
13. Davies, R., Bell, B. R., Cartwright, J. A. & Shoulders, S. *Geology* **30,** 223–226 (2002).
14. Graue, K. *Mar. Petrol. Geol.* **17,** 959–974 (2000).
15. Dimitrov, L. I. *Earth Sci. Rev.* **59,** 49–76 (2002).

Neurobiology

A matter of balance

Martyn Goulding

The types of chemical signal that a neuron synthesizes and communicates with were thought to be genetically encoded and largely invariable. It seems, though, that if a neuron's activity changes, so too do its signals.

Nerve cells use chemical signals known as neurotransmitters to communicate with each other. These molecules come in many different flavours, and the combination of flavours used by any given neuron represents a key property that determines not only its function within a circuit, but also the circuit's overall output. How exactly neurons regulate the profile of neurotransmitters that they express — their neurotransmitter 'phenotype'— is poorly understood, although it is known that most neurons synthesize a highly restricted repertoire of neurotransmitters, and that the regulatory events governing this repertoire occur in the embryo, soon after a neuron is born and begins to take on a particular identity. Numerous studies[1–4] have also led to the view that a neuron's transmitter phenotype is tied closely to the genetic programme that controls its developmental fate, such that a neuron's identity and its neurotransmitter profile are inextricably interwoven.

On page 523 of this issue[5], however, Borodinsky and colleagues challenge this view. These authors provide evidence that, in the spinal cord of developing frogs, profiles of neurotransmitter expression can change in response to differing degrees of neuronal activity. Although it was well known that neurons can alter the *levels* of expression of particular neurotransmitters after changes in circuit activity, what is interesting about the new study is that it shows that embryonic spinal-cord neurons can also alter the *types* of neurotransmitter that they produce — and that they do this independently of changes in cell identity. Moreover, these changes in neurotransmitter phenotype, which seem to be encoded by the patterns of Ca^{2+} spikes — a measure of activity — that the neurons produce, occur in a system that was thought to be genetically 'hardwired'.

Previously, patterns of Ca^{2+} spikes were shown to modulate the expression of neurotransmitters *in vitro*[6]. Borodinsky *et al.*[5] have now taken an elegant approach to assessing the role of Ca^{2+}-dependent activity in neurotransmitter expression *in vivo*. First, they noted that different populations of embryonic neurons exhibit distinctive patterns of Ca^{2+} spikes. Then they studied the effects of experimentally manipulating this activity, by engineering the developing spinal cord to overexpress one of two types of ion channel: a potassium channel that hyperpolarizes neurons and so reduces Ca^{2+} spike activity, or a sodium channel that increases the frequency of spike activity. By injecting messenger RNA transcripts encoding one of these channels at the two-cell stage of embryonic

100 YEARS AGO

In the course of an interview reported in the *Westminster Gazette* of Friday last, Lord Kelvin is reported to have expressed himself as being decidedly of the opinion that the source of energy of the heat emitted by radium is not in the element itself. He remarked:— "It seems to me absolutely certain that if emission of heat at the rate of 90 calories per gram per hour found by Curie at ordinary temperature, or even at the lower rate of 38 found by Dewar and Curie from a specimen of radium at the temperature of liquid oxygen, can go on month after month, energy must somehow be supplied from without."

ALSO

A Reuter message from Wellington, New Zealand, reports that the King has sent the following telegram to Captain Scott, leader of the National Antarctic Expedition:— "I have read with interest your report, which Sir Clements Markham sent me. I congratulate you and your gallant crew on your splendid achievements, and wish the *Discovery* a safe journey home. I hope to see you on your return to England."

From *Nature* 2 June 1904.

50 YEARS AGO

It is no bad thing that a broadsheet entitled "Graduate wives"… has provoked considerable discussion regarding the value of university education for women, and perhaps more particularly when that education has only been possible because of the help received from public funds in some form or another. That latter point was not specifically covered by the inquiry, although it is noted that many thousands of pounds of public money are spent on the education of the four thousand women graduates who leave the universities of Great Britain every year... the fact that the majority of those covered by this inquiry made no direct use of their academic qualifications after marriage does not imply that the public money expended on their university education has been wasted, though it may well induce some re-examination of the system of university awards and a fuller consideration of the whole purpose of university education. As the broadsheet points out, the indirect contribution which a trained mind and cultured outlook can make to family life and to the life of the nation generally is very great indeed.

From *Nature* 5 June 1954.

development, the authors could manipulate spike activity in either one or both halves of the spinal cord when it formed later on in development.

Intriguingly, they find that a decrease in Ca^{2+} spike activity is correlated with an increase in the number of neurons that produce marker proteins indicative of the expression of glutamate and acetylcholine — two types of excitatory neurotransmitter. In contrast, increased spike activity results in fewer cells expressing these neurotransmitters. Similarly, in their initial experiments Borodinsky *et al.* found that, at early stages of development, motor neurons — which produce acetylcholine — normally generate a low frequency of spike activity. Meanwhile, ventral interneurons, another type of nerve cell, show a high rate of activity and produce little acetylcholine. But when sodium channels were overexpressed in nerve cells that include inhibitory commissural neurons, more ventral interneurons expressed ChAT, the enzyme that catalyses acetylcholine production. This presumably reflects a decrease in the frequency of Ca^{2+} spikes in these ventral interneurons, because of increased inhibition by commissural neurons that are generating more spikes than usual.

The authors also observe reciprocal changes in the expression of the inhibitory neurotransmitters γ-aminobutyric acid (GABA) and glycine, such that fewer neurons express these neurotransmitters when Ca^{2+} spike activity is low, and more neurons do so when spike activity is high. Remarkably, increases and decreases in activity also result in excitatory and inhibitory neurotransmitters being expressed at the same time in some neurons. Somewhat surprisingly, none of these changes affect the expression of certain markers of neuronal identity, suggesting that a neuron's identity and its neurotransmitter phenotype are not strictly linked. Together, these findings suggest that a homeostatic mechanism, one that attempts to maintain the status quo, regulates the overall level of neuronal activity in the embryonic spinal cord.

An indication that these activity-dependent changes might be important in normal development comes from the authors' observation that there is an essential period during which Ca^{2+} spike activity is required for altered neurotransmitter expression — a phenomenon seen in other systems in which neural activity regulates circuit formation. Nevertheless, the extent to which activity controls neurotransmitter expression during normal development remains to be seen. Although Borodinsky and colleagues' results show that perturbations in Ca^{2+} spike activity can clearly, in an experimental set-up, override the genetic programme that determines neurotransmitter phenotype, the authors of another recent study[3] argue that a genetically hardwired programme operates in the mouse spinal cord to direct the formation of glutamate-producing as opposed to GABA-producing neurons.

Borodinsky *et al.* further show that activity-related changes in neurotransmitter expression also occur in isolated neurons *in vitro*, hinting that a cell-autonomous mechanism — a mechanism that depends solely on the neuron in question, and not on external factors — regulates neurotransmitter output. So is the activity-dependent regulation of neurotransmitter expression a property of individual neurons, or of the circuit to which they contribute, or both?

Interestingly, the neurons that exhibit activity-induced changes in frogs are constituents of the primary nervous system that controls larval swimming and escape reflexes. As these circuits develop very early, and are 'wired-up' during the essential period of Ca^{2+} spike activity, one could imagine a mechanism that operates to calibrate the overall activity of neurons in this circuit, and thus ensure that larval movements are properly coordinated. In embryos that do not use such motor behaviours, this aspect of regulation might be missing. Furthermore, as GABA and glycine are initially excitatory in the spinal cords of birds and mammals, changes in the expression of these neurotransmitters would not necessarily alter the balance between excitation and inhibition.

These findings[5] raise several additional questions. First, how widespread is this mechanism of activity-dependent neurotransmitter regulation? Second, how do activity-dependent regulatory pathways interface with the genetic programmes that control neurotransmitter phenotype? Third, what is the underlying molecular mechanism that translates Ca^{2+} spike activity into changes in neurotransmitter expression? Last, are alterations in neurotransmitter expression matched by alterations in the expression of their cognate receptors on downstream neurons? Clearly there is a lot more to know about the role of activity and Ca^{2+} signalling in neuronal differentiation. Nonetheless, Borodinsky and colleagues' study indicates that concentrating solely on the molecular and genetic mechanisms that control neurotransmitter expression will cause us to overlook some of the essential pathways that configure neural circuits. ■

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1. Goridis, C. & Rohrer, H. *Nature Rev. Neurosci.* **3,** 531–541 (2002).
2. Hendricks, T. J. *et al. Neuron* **37,** 233–247 (2003).
3. Cheng, L. *et al. Nature Neurosci.* **7,** 510–517 (2004).
4. Pattyn, A. *et al. Genes Dev.* **17,** 729–737 (2003).
5. Borodinsky, L. *et al. Nature* **429,** 523–530 (2004).
6. Watt, S. D., Gu, X., Smith, R. D. & Spitzer, N. C. *Mol. Cell Neurosci.* **16,** 376–387 (2000).

Behavioural genetics

All in the family

Allen J. Moore

Mothers and offspring may have different ideas about how much maternal care should be provided. How is the behaviour of both parties genetically influenced, and how is this evolutionary conflict resolved?

Family conflicts are of professional interest not only to agony aunts but to evolutionary biologists as well. A case to exercise the latter has just appeared in *Proceedings of the Royal Society*[1], where James Curley and colleagues describe their manipulations of a mouse gene, *Peg3*. This gene is of particular interest because it is known to influence maternal behaviour, but is also inherited in an unusual fashion.

Conflicts between mother, father and offspring take several forms. Newborns in a species that provides parental care often demand more than a mother is willing to give. The interest of the mother is to ensure that the needs of her offspring are met while retaining the ability to take care of other or future offspring; the interest of an offspring is to get as many resources as possible for itself, regardless of the interests of its siblings or mother. Fathers' interests may coincide with those of the offspring, particularly if there is uncertainty that he will father other or future offspring in this family and the mother provides all the care. Conflicting selection pressures can therefore arise. If the behaviour is genetically influenced, that raises questions about how such family conflicts are resolved over evolutionary time[2].

Curley and colleagues[1] have applied modern techniques to investigate the genetics of such conflicts in mice. The *Peg3* gene they studied is paternally expressed: that is, the mother's copy of the gene is turned off in the offspring. This phenomenon, known as 'imprinting', is predicted to have evolved in genes whenever there are asymmetries in the evolutionary interests of parents in the behaviour directed towards offspring[3]. But whose behaviour is affected? Is the action of *Peg3* expressed in mothers or in offspring?

Because individuals only express the *Peg3* gene they inherit from their father, it is possible to generate mouse families in which the mother expresses the functional *Peg3* gene product but the offspring don't, and vice