epochs. From the NIR emission, they derived a mass of dust equivalent to 830 Earth masses, which is 40 times lower than observed in the ancient Crab Nebula supernova remnant[9]. Such a small dust mass is unsurprising, given the relative youthfulness of SN 2010jl.

As well as measuring the quantity of freshly formed dust, Gall *et al.* used their data to graphically show the extent of the absorption of light by the dust grains as a function of wavelength — the extinction curve. This curve provides information on the dust composition (carbon-rich in this case) and size distribution, and reveals perhaps the most significant result from this work: newly formed supernova dust grains are gigantic compared with dust typically found in our Galaxy. The same type of analysis for the Milky Way requires dust grains with a maximum size of 0.25 micrometres to reproduce the observed extinction curve, but in SN 2010jl, the grains need to be greater than 1 μm with a maximum grain radius of 4.2 μm.

The presence of such large grains in a distant supernova is at odds with the size distribution assumed in theoretical dust models used in the literature[13]. However, this is not the first time that astronomers have observed large grains. The Ulysses robotic spacecraft mission[14] recorded substantial emission from grains larger than 2 μm entering our Solar System, and grains as large as 6 μm were detected hitting our planet's atmosphere[15]. Similarly large dust grains have also been seen in distant γ-ray bursts[16].

These large grains seen in our Solar System, and now in an extragalactic supernova, imply not only that is dust created directly as a result of the explosion, but also that supernova dust might be hardy enough to survive the explosion's harsh environment. Owing to their size, larger grains will be more resilient to high-speed collisions compared with smaller grains, and could well survive the explosion in the long term, albeit chipped into smaller pieces as they make their way into the surrounding gas.

Another supernova (SN 1987A) in the nearby Large Magellanic Cloud, a satellite galaxy of the Milky Way, perhaps provides researchers with an ideal laboratory to directly measure the efficiency of dust destruction in supernova shocks. The debris of SN 1987A[10,11] is currently moving at 2,000 kilometres per second, and will soon collide with a ring of material left over from the progenitor star before the explosion. Astronomers will be able to observe with ALMA the thermal emission from the dust as the supernova ejecta and the ring collide in real time. Such observations will detect an evolution in dust formation and destruction even at a distance of 50,000 parsecs (the distance from Earth at which the debris of SN 1987A is located). If collisions do prove to be less destructive than theoretical models currently suggest, this will be comforting news to astronomers trying to explain the large dust masses observed in galaxies[6,7,17]. It seems that supernovae may not be the bad guys after all. ■

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NEUROBIOLOGY

Keeping a lid on it

The protein Npas4 dampens activated excitatory brain circuits by recruiting inhibitory signals to excitatory neurons. It emerges that this protein has the opposite role in some inhibitory neurons, promoting their activity.

GINA TURRIGIANO

The astounding abilities of the mammalian brain arise from a few core circuit 'motifs'. One such motif is positive feedback[1], in which the mutual excitation of pyramidal neurons amplifies small signals. Now, fans of rock legend Jimi Hendrix will immediately recognize the problem this raises: positive-feedback amplification can easily get out of control, and an effect that is awesome in 'Voodoo Child' can lead to epilepsy in brain circuits. Our brains must therefore counteract positive feedback with inhibitory circuit motifs — pyramidal neurons excite several subtypes of inhibitory neuron, which then inhibit those same pyramidal neurons through negative feedback (Fig. 1a). One mystery is how these circuits are adjusted to maintain the excitation–inhibition balance in the brain[2]. Writing in *Cell*, Spiegel *et al.*[3] provide insight into this homeostatic balancing act, showing how gene-expression pathways that regulate neuronal circuits are differentially tuned to the function of inhibitory and excitatory motifs.

During development, neuronal identity is determined by the restriction of gene expression to a subtype-specific pattern[4]. However, gene expression does not then remain static. For our brains to learn and adapt, neurons

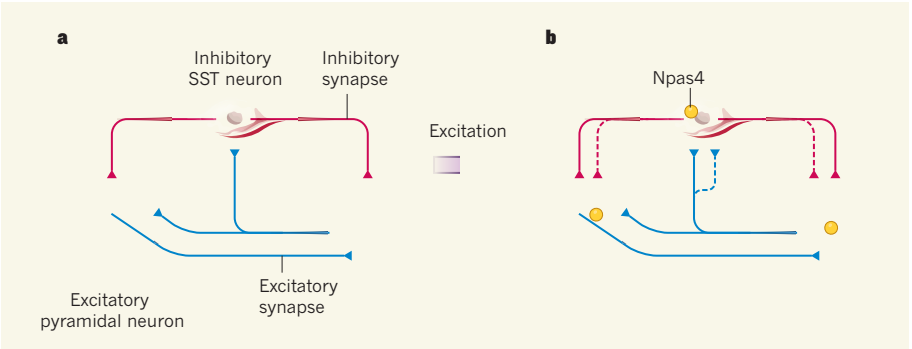

Figure 1 | Balancing excitation levels. **a**, Excitatory pyramidal neurons transmit signals to inhibitory somatostatin-positive (SST) neurons, and vice versa, through neurotransmitting junctions called synapses. In addition, excitatory neurons synapse to one another in a positive feedback loop. **b**, Spiegel *et al.*[3] report that neural excitation induces expression of the transcription factor Npas4 in both cell types, triggering neuron-specific gene programs. Npas4 expression in SST neurons causes an increase in the number of excitatory synapses to these neurons (blue dashed synapse). Conversely, Npas4 expression in pyramidal neurons increases their inhibition (red dashed synapses). Overall, these dynamic changes dampen excitation.

must respond to changes in the environment, and this dynamism arises in part through activity-dependent changes in gene-expression pathways[5]. These changes are thought to control activity by, for example, adjusting the effectiveness of excitatory and inhibitory synaptic connections (junctions between neurons that transmit information) in a manner that is specific to both cell and synapse type[6]. For instance, too much activity boosts the effectiveness of inhibitory synapses acting on excitatory neurons, dampening excitation. Conversely, too little activity increases the effectiveness of excitatory synapses acting on excitatory neurons. Thus, homeostatic plasticity follows a 'circuit logic' that coordinately adjusts excitatory and inhibitory feedback loops to stabilize neuron firing[6].

Spiegel and colleagues set out to identify genes that contribute to such neuronal-subtype-specific adjustments. To do this, they generated neuronal cultures that were enriched in either inhibitory or excitatory neurons. When the authors depolarized the cultures (which mimics excitation), the two cell types displayed similar early changes in gene expression. In particular, the expression of several early-response genes, including *Npas4*, was increased in both cultures.

Things got interesting when Spiegel and co-workers turned their attention to the late response to depolarization. After six hours, there was a substantial increase in the number of genes whose expression was modified, but the fraction of modified genes that was shared by inhibitory and excitatory neurons was smaller than during the early response. The authors then confirmed these results *in vivo* using an approach that allowed them to probe gene expression in a cell-type-specific manner. Taken together, their results suggest that enhanced activity triggers a shared early transcriptional program in excitatory and inhibitory neurons, which then sets in motion distinct downstream signalling pathways.

The early-response gene *Npas4* caught Spiegel and colleagues' attention because the transcription factor that it encodes[7] acts to promote homeostasis in excitatory pyramidal neurons by regulating the number of inhibitory synapses they receive[8]. The authors wondered whether Npas4 might have a different function in inhibitory neurons, because enhancing inhibition onto inhibitory neurons would have the paradoxical effect of activating pyramidal neurons — a counterproductive effect for homeostasis.

To test this, Spiegel *et al.* manipulated Npas4 expression in somatostatin-positive (SST) inhibitory neurons, which mediate a type of feedback inhibition in the brain. Selectively removing Npas4 from SST neurons in brain slices or in cultures containing both inhibitory and excitatory cell types had no effect on the number of inhibitory synapses to SST neurons, but decreased excitatory synapses. Conversely, overexpressing Npas4 in SST neurons increased excitatory synapses to those neurons. Furthermore, the authors found that Npas4 deletion compromised the expression of a subset of late-response genes in SST neurons, but that Npas4 overexpression promoted expression of these same genes.

Spiegel *et al.* therefore conclude that enhanced neuronal activity activates Npas4 in both cell types. This sets in motion different late-response transcriptional programs that have distinct outcomes — increased excitation of SST neurons and increased inhibition of pyramidal neurons. These two Npas4-mediated gene programs would be expected to synergize, overall inducing increased inhibition of pyramidal neurons and thus counteracting a rise in activity (Fig. 1b).

Although the model is appealing, it is important to bear in mind that brain circuits contain several subtypes of inhibitory neuron, and that the SST–pyramidal circuit is only one of many feedback loops that regulate excitability[1]. Whether the changes measured here contribute significantly to circuit homeostasis remains unknown.

A second caveat is that, although the model predicts that raising activity should increase excitatory synapses to SST neurons in an Npas4-dependent manner, Speigel and colleagues did not test this prediction directly. Despite the fact that directly reducing or increasing Npas4 expression does modulate synapse number, the effects of Npas4 when manipulated alone may be different from its effects in the context of other activity-induced genes. As such, experiments that confirm the authors' model seem key.

Finally, the study raises the fundamental question of how Npas4 regulates distinct genes in different cell types. Spiegel *et al.* find a partial answer — regulatory DNA elements that control the expression of Npas4 target genes are in different epigenetic states in the two cell types (epigenetic regulation changes gene expression without altering DNA sequence). This suggests that gene programs underlying homeostasis are epigenetically tuned to the function of each neuron within a neural circuit.

So if listening to Hendrix amps your brain circuits up to 11, don't worry. Dynamic negative feedback loops, working through cell-type-specific effectors such as Npas4, are there to keep a lid on things. ■

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CANCER

Sugar-coated cell signalling

Cell membranes are covered with sugar-conjugated proteins. New findings suggest that the physical properties of this coating, which is more pronounced in cancer cells, regulate cell survival during tumour spread. SEE ARTICLE P.319

ANDREW J. EWALD & MIKALA EGEBLAD

The cell membrane serves as a signalling interface that allows cells to exchange information with their environment. It is constructed from lipids and contains both transmembrane and lipid-tethered proteins, which can be further modified through the covalent addition of sugars to build glycoproteins. Cancer cells frequently have higher levels of glycoproteins, such as mucin-1 (refs 1–3), than do healthy cells, and individual glycoproteins can transduce environmental signals that directly promote malignancy. However, glycoproteins also collectively organize into a glycocalyx. In this issue, Paszek *et al.*[4] (page 319) show how the physical properties of this coating regulate the clustering of cell-surface receptors and thereby affect intracellular signalling in ways that can contribute to cancer metastasis.

The authors demonstrate that the thickness of the glycocalyx is a crucial determinant of the spatial and temporal features of receptor–ligand interactions. Specifically, they find that the thick glycocalyx of cancer cells serves as