normally associated with benzodiazepines — the recruitment of new AMPA receptors to glutamatergic synapses on dopaminergic neurons. This result suggested that, despite differences in their binding sites, benzodiazepines and opioids ultimately share the same interneuron target. The authors therefore reasoned that benzodiazepines, like opioids, might increase the excitability of dopaminergic neurons by reducing interneuron-mediated inhibition, a process known as disinhibition.

Tan *et al.* tested this theory by sampling VTA dopaminergic cells from brain slices and recording the inhibitory currents mediated by $GABA_A$ receptors in these cells. In tissue from wild-type mice, they observed that a typical benzodiazepine (midazolam) reduced the inhibitory current in dopaminergic neurons, in line with the disinhibition hypothesis. Conversely, in α1-mutated mice, the inhibitory currents in dopaminergic cells increased in response to the drug, suggesting that benzodiazepines reduce the release of GABA in wild-type mice.

The authors went on to record the activity of VTA neurons *in vivo*, and noted that, in wild-type mice, benzodiazepines simultaneously activated dopaminergic neurons and inhibited GABAergic interneurons. This disinhibition effect was reversed when the authors subsequently administered a benzodiazepine antagonist to the animals. What's more, disinhibition was altogether absent in α1-mutated mice.

Finally, the researchers studied how prone their mice were to self-administering benzodiazepines. When given a choice between drinking either a sugar solution or a sugar solution laced with midazolam, wild-type mice preferred the midazolam-containing solution. The α1-mutated mice, however, showed no such preference, even though they drank as much liquid overall as the wild-type animals, and preferred sugar solution to pure water (indicating that they were capable of reward-motivated discrimination).

Taken together, Tan and colleagues' data[1] suggest that the activation of α1-containing $GABA_A$ receptors by benzodiazepines calms GABAergic interneurons, reducing their overall inhibitory output. Consequently, dopaminergic neuron firing increases in the VTA, which elevates the number of AMPA receptors in the membranes of the excited dopaminergic neurons and strengthens the excitatory synapses that favour addiction (Fig. 1). This general disinhibition mechanism is analogous to that involved in opioid drug abuse[3].

More studies are required to fully appreciate the context of the proposed mechanism[1]. For example, synaptic scaling — a homeostatic process that adjusts the strength of a neuron's excitatory synapses up or down to stabilize firing[4,5] — also modulates the number of AMPA receptors in neuron membranes, but its relevance in the VTA isn't clear and will be challenging to determine. Another consideration is that both dopaminergic and GABAergic cells receive GABAergic innervation, and the distribution of α1-containing $GABA_A$ receptors in these systems is both presynaptic and postsynaptic. This somewhat ambiguous distribution suggests that additional α1-dependent mechanisms of addiction might exist in which benzodiazepines modulate the excitability of dopaminergic cells.

Other findings indicate that benzodiazepine abuse is not always attributable to α1-containing $GABA_A$ receptors. For example, it is unclear why the overall incidence of zolpidem addiction is low relative to that of less-selective benzodiazepines (those that, unlike zolpidem, show no binding preference for α1 GABA subtypes), opioids or other drugs of abuse[6]. It is also unclear why primates will self-administer[7] a benzodiazepine known as L-838 417, which binds to, but does not activate, α1-containing $GABA_A$ receptors and (as Tan *et al.*[1] show) does not change AMPA-receptor distribution in dopaminergic neurons.

Nevertheless, Tan and colleagues' discovery[1] is a landmark for the field — these authors are the first to identify a molecular mechanism contributing to benzodiazepine abuse. Given that the α1 subunits of $GABA_A$ receptors are not responsible for the therapeutic effects of benzodiazepines[8], the work highlights an exciting possibility: if benzodiazepines can be designed that lack affinity for this subunit, then the addictive properties of these versatile and useful drugs might be reduced. ■

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PARKINSON'S DISEASE

Mitochondrial damage control

Asa Abeliovich

Defects in mitochondria are implicated in Parkinson's disease. Study of a quality-control pathway involving the proteins PINK1 and Parkin provides further clues about the mechanism involved.

The pursuit of a unifying mechanism for Parkinson's disease has been refuelled by the identification of genetic mutations that underlie inherited variants of the disorder[1]. For instance, mutants of a particular enzyme — the mitochondrial PTEN-induced kinase-1 (PINK1) — cause a rare, early-onset form of Parkinson's[2], directly implicating altered mitochondrial regulation in the disease process. Furthermore, mice with mutations in PINK1 display reduced mitochondrial function[3]. Mitochondria are double-membrane-bound organelles that produce energy in the form of ATP, but in the course of this process they can accumulate toxic by-products as well. They are thus crucial to a cell's well-being — as is their disposal when they malfunction.

Writing in *PLoS Biology*, Narendra *et al.*[4] now describe a specific role for PINK1 in mitochondrial quality control and disposal. The authors observe that PINK1 accumulates within minutes at mitochondria that have lost the electric-potential gradient that spans their inner membrane, as is seen on exposure to mitochondrial poisons or in ageing. Such poisons have been linked epidemiologically to Parkinson's disease[5]. Whereas normal cells that are exposed to these depolarizing toxins eventually dispose of the damaged mitochondria, Narendra *et al.* find that cells deficient in PINK1 (or with disease-associated mutant forms of PINK1) fail to do so.

As the authors point out, reactive oxygen species or other damaging agents may leak from damaged mitochondria. This suggests a mechanism for the loss of midbrain neurons that produce dopamine neurotransmitter — a defining feature of Parkinson's disease. The accumulation of defective mitochondria might in part explain other features associated with mutation in the *PINK1* gene, such as altered mitochondrial morphology[6] and reduced ATP production. In contrast to PINK1 deficiency, overexpression of the normal protein promotes mitochondrial loss, further implicating PINK1 in the disposal process.

These findings shed light on a study from the same group[7] that focused on *parkin*, a second gene that is mutated in an inherited form of Parkinson's disease. The Parkin protein occurs mainly in the cell cytoplasm, but re-localizes to mitochondria that have been treated with depolarizing agents. Cells that are deficient in Parkin, or that have disease-associated Parkin mutations, fail to rid themselves of defective mitochondria; by contrast, Parkin overexpression induces excessive mitochondrial disposal, reminiscent of

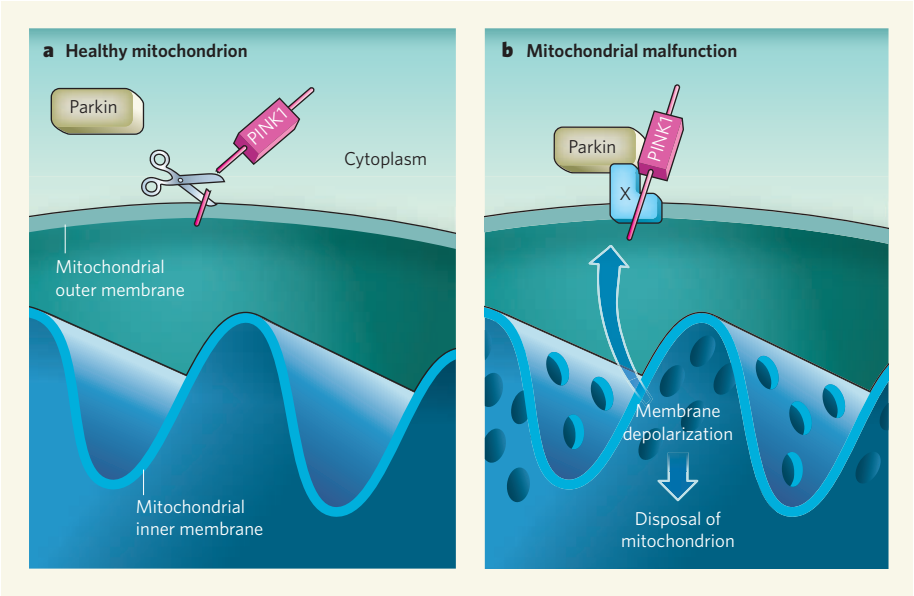

Figure 1 | Possible mechanism of mitochondrial monitoring by PINK1 and Parkin. The following scheme is consistent with the results of Narendra and colleagues[4]. **a,** In healthy mitochondria, PINK1 is maintained at low levels because it is cleaved by an unidentified protease. **b,** When a mitochondrion malfunctions, with associated depolarization of the membrane electrical-potential gradient, PINK1 is stabilized at the outer mitochondrial membrane with its kinase domain facing the cytoplasm. Directly or indirectly through an unknown protein, X, PINK1 then recruits Parkin to the mitochondrial surface, inducing disposal of the damaged organelle.

the outcome of PINK1 overexpression.

Remarkably, the recruitment of Parkin to depolarized mitochondria depends on the presence of normal, full-length PINK1[4], pointing to the existence of a regulatory pathway for mitochondrial quality control that links PINK1 and Parkin (Fig. 1). This link is supported by genetic studies in the fruitfly *Drosophila*[8,9]. But the precise molecular nature of the relationship remains to be established. As PINK1 seems to span the outer mitochondrial membrane, with its kinase domain on the cytoplasmic side[10], direct physical contact with Parkin at the cytoplasmic surface of mitochondria is conceivable. However, Parkin does not seem to be the target of PINK1 kinase activity[4,11]; and PINK1 does not seem to be modified by Parkin's enzymatic activity as a ubiquitin ligase, which can target substrates for degradation. If PINK1 and Parkin do not interact directly, perhaps PINK1 regulates a mitochondrial receptor for Parkin such as the voltage-dependent anion channel-1 (VDAC-1)[12].

Once tagged by Parkin and PINK1, the disposal of depolarized or otherwise defective mitochondria may proceed through a process, termed macroautophagy, that is typically induced in the context of nutrient starvation or toxic stressors[13]. Alterations in this disposal pathway have been linked to Parkinson's disease in previous genetic and pathological studies. Narendra *et al.*[4] further reveal that mutant forms of Parkin can impede either the initial translocation of Parkin to mitochondria or the subsequent induction of the macroautophagy disposal process.

How might Parkin trigger this process? Macroautophagy is negatively regulated by a signalling pathway involving the PI3K/Akt enzymes and mediated by the 'target of rapamycin' (TOR) kinase. But the role of TOR signalling in mitochondrial disposal, and whether Parkin functions through this pathway, remain unclear. Remarkably, pharmacological inhibition of TOR using rapamycin can suppress the pathological effects of Parkin and PINK1 in *Drosophila*[14]. However, it seems that this protective effect is multifactorial: TOR inhibition also reprograms the protein-translation machinery to favour the expression of mitochondrial and stress-responsive proteins[15].

Among other questions demanding answers is how mutations in ubiquitously expressed genes lead primarily to the loss of neurons in the midbrain. The reason may be that mitochondria are exposed to oxidative stress as a by-product of dopamine metabolism, or that there is a problem in maintaining mitochondria in the elongated processes of these neurons. Finally, there is the issue of how closely the rare inherited forms of Parkinson's disease relate to the common 'sporadic' syndrome[1]. A combination of minor genetic or environmental risk factors may impinge on the PINK1–Parkin pathway illuminated by Narendra *et al.*[4,7] and by others. But this, too, is a possibility that requires further investigation. ■

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ASTROPHYSICS

Less greedy galaxies gulp gas

Andrew Blain

The cool molecular gas from which stars form has been detected in relatively ordinary faraway galaxies. The results point to a continuous fuelling of gas into the star-forming guts of assembling galaxies.

Stars form in the regions of galaxies that are the hardest to observe with many of the common tools of astronomy — in dense, cool (10–100 K) clouds of molecular gas from which only a small fraction of visible light can escape. Once stars form, the pressure of their radiation expels this gas, and they can then be seen clearly at optical wavelengths. Directly imaging the gas that fuels star formation requires observations of the radiation emitted by rotating or vibrating molecules at long and short infrared wavelengths, respectively, where the clouds are more transparent. However, only polarized molecules, such as carbon monoxide (CO), emit strong rotational spectral lines: the bulk of gas mass remains invisible in the form of molecular hydrogen. Nevertheless, the measured width and shape of the CO spectral lines can be combined with assumptions about the distribution of emitting gas, along with all the gravitating matter in the galaxy that controls the motion