Parkin ubiquitinates various proteins, promoting their degradation. Some of these target proteins (for example, mitochondrial assembly regulatory factor (MARF)) stabilize contacts between the endoplasmic reticulum (ER) and mitochondria. Here, the authors found that the LNvs and IPCs from mutant flies and induced hypothalamic neurons from individuals with PD exhibited a greater ER–mitochondria contact surface than did control neurons. Overexpression of MARF in LNvs of wild-type flies increased ER–mitochondrial contacts and reduced morning anticipation. Thus, the increase in ER–mitochondrial contacts in the pink1- or park-mutant flies may cause the circadian deficits in these animals.

ER–mitochondrial contacts facilitate ER-to-mitochondrion transfer of PtdSer, which is enriched in DCV membranes. Compared with controls, the mitochondria and ER of park-mutants contained more and less PtdSer, respectively. Moreover, knockdown of PtdSer synthase in LNvs phenocopied the neuropeptide-distribution and morning-anticipation deficits observed in *park* mutants. Strikingly, supplementing *park* and *pink1* mutants with PtdSer for a few days rescued neuropeptide-distribution defects in LNvs and IPCs, and ameliorated circadian deficits. Therefore, increasing ER–mitochondrial contacts reduces ER PtdSer levels, in turn leading to circadian deficits.

Together, these results provide a possible mechanism underlying circadian deficits in certain forms of PD. Loss of parkin function results in an increase in ER–mitochondrial contacts, which in turn depletes PtdSer levels in ER and may affect the formation of DCVs containing neuropeptides.

Natasha Bray

ORIGINAL ARTICLE Valadas, J. S. et al. ER lipid defects in neuropeptidergic neurons impair sleep patterns in Parkinson's disease. *Neuron* https://doi.org/10.1016/j.neuron.2018.05.022 (2018)

a number of pro-inflammatory genes being upregulated.

Next, the authors co-cultured their iPSC-derived microglia-like cells with cerebral organoids that were generated from iPSC lines carrying an amyloid precursor protein duplication (APP^{DP}); these organoids develop Aβ aggregates and other AD hallmarks within 2–3 months. APP^{DP} organoids co-cultured with APOE4-carrying microglia-like cells exhibited more extracellular Aβ aggregates than controls and the microglia-like cells exhibited long processes, a phenotype negatively associated with microglial Aβ uptake. The authors then generated organoids from their isogenic APOE3 or APOE4-containing iPSC lines. At 6 months, APOE4 organoids showed higher Aβ accumulation and less APOE proteins than controls.

Finally, the authors tested whether the molecular and cellular AD phenotypes described above could be reversed by converting APOE4 into APOE3 in iPSCs from a patient with sporadic AD. They used a CRISPR–Cas9 approach to generate isogenic homozygous APOE3-containing iPSCs from homozygous APOE4-containing iPSCs, and generated neurons, microglia, astrocyes and organoids as before. The APOE3-carrying neurons showed reduced mEPSCs and fewer synapses but no difference in secreted Aβ42. In astrocytes and microglia, the APOE4 into APOE3 switch resulted in increased Aβ uptake. In cerebral organoids after 6 months of culture, APOE3 organoids showed less Aβ accumulation compared with age-matched APOE4 organoids, overall indicating that many of the AD-related phenotypes observed in APOE4-derived cells can be ameliorated by editing to APOE3.

Together, these findings provide insight into the cellular mechanisms by which the APOE4 variant might contribute to human AD pathology.

Sian Lewis

ORIGINAL ARTICLE Lin, Y.-T. et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron* **98**, 1–14 (2018)

REWARD

Treasure hunt

Credit: J. Vallis/Springer Nature Limited

Learning to navigate towards a goal location involves both spatial memory and reward (goal) encoding, and hippocampal pyramidal cells play roles in both. How goal location is encoded is not well understood, but here, Gauthier and Tank identify a subpopulation of cells in hippocampal CA1 and subiculum that are dedicated to this role.

The authors designed a virtual reality task in which head-fixed mice ran on a linear track while a virtual environment was projected on a surrounding screen. This set-up allowed water-restricted mice to be trained to 'traverse' this virtual environment towards a particular location where they would receive a water reward (the goal); neural activity in CA1 and subiculum was monitored simultaneously using two-photon imaging.

As expected, in both subiculum and CA1 the authors found numerous cells that respond differently depending on position on the track, with a greater density of place fields occurring near the reward location. Although the place fields of most cells remained the same when the location of the reward was changed, a few cells tracked the new reward location. The authors determined that these cells constituted a small, discrete population of cells separate from place cells, which they termed reward-associated cells (RACs). RACs consistently produced reward-associated responses across different virtual environments and accounted for the increased density of cell responses near the reward location.

Within this population, some fired before the reward (reward-predictive cells, RPCs), and when the reward location and/or environment was changed, the sequence of activation and timing of RPCs remained highly consistent, suggesting that these cells are highly specialized for encoding reward location.

RPC firing in both CA1 and subiculum coincided with anticipatory behaviours, such as slowing down on approach to the reward location and anticipatory licking. The authors found that RPC firing at the current reward location was approximately five times greater than at a previously-trained reward location, whereas anticipatory behaviours were similar at both locations, suggesting that RPCs do not directly encode behaviour.

Overall, these data reveal a population of cells in both subiculum and CA1 that encode the location of a reward with high consistency, even when the location or environment containing the reward changes.

Sian Lewis

ORIGINAL ARTICLE Gauthier, J. L. & Tank, D. W. A dedicated population for reward coding in the hippocampus. *Neuron* https://doi.org/10.1016/j.neuron.2018.06.008

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