IN THE NEWS

Will you still love me in the morning?

On being accused of drunkenness by fellow politician Bessie Braddock, the British prime minister Winston Churchill is quoted as replying "And you are ugly, but at least I shall be sober in the morning". Clearly, Churchill had not succumbed to the 'beer goggles' effect; otherwise he might have viewed his colleague in a more favourable light.

Many of us are aware of beer goggles — the invisible optical aids that make members of the opposite sex appear more attractive after a few drinks — but until recently, the phenomenon had not been subjected to the rigours of scientific experiment. However, Barry Jones, a psychologist from the University of Glasgow, has set out to change all that ("Beauty is in the eye of the beerholder", *BBC News*, 18 August).

In his experiment, Jones showed students 120 photographs of men and women, and asked them to judge their attractiveness on a scale from one to seven — seven being the most attractive. He discovered that, on average, the students who had drunk a moderate amount of alcohol found the people 25% more attractive than did those in the sober control group.

Jones related his new findings back to one of his previous studies, saying "What we may have here is an explanation for why moderate doses of alcohol increase the chance of unprotected sex. It might be because the alcohol makes the person's partner seem more attractive" (*Scotland on Sunday*, 18 August).

Professor Geoff Palmer, from Heriot-Watt University's International Centre for Brewing and Distilling, had a more straightforward view: "This research confirms what many drinkers already know; the world seems a hell of a lot better after a couple of pints" (*Scotland on Sunday*).

Heather Wood

NEURODEGENERATION

Autophagy lurks around lurcher

Lurcher mice suffer from cerebellar degeneration owing to a mutation in the ionotropic glutamate receptor subunit δ2 (GluRδ2). This mutation leads to constitutive receptor activation, causing persistent cation entry into Purkinje cells. Ion influx is widely believed to cause neuronal death in lurcher mice, but Yue *et al.* now provide compelling evidence that autophagy is responsible for Purkinje cell death in these animals.

Autophagy is a process whereby cells digest their own cytoplasm during starvation. Morphologically, autophagy is characterized by the rearrangement of intracellular membranes and the formation of vacuoles that deliver cytoplasmic elements to lysosomes. Molecularly, autophagy involves proteins such as Apg6 in yeast. Beclin 1 is the vertebrate orthologue of Apg6, and Yue *et al.* found that this protein interacts with a new protein called nPIST, which in turn can bind GluRδ2.

Using a two-hybrid screen to identify binding partners of GluRδ2, the authors isolated nPIST and established that it is expressed in the cerebellum. Moreover, GluRδ2 and nPIST co-fractionated in cerebellar extracts and were enriched in the postsynaptic density. But because the function of nPIST is not known, Yue *et al.* performed a second screen to identify partners of this protein, isolating beclin 1 and subsequently showing that the three proteins form a complex in the cerebellum.

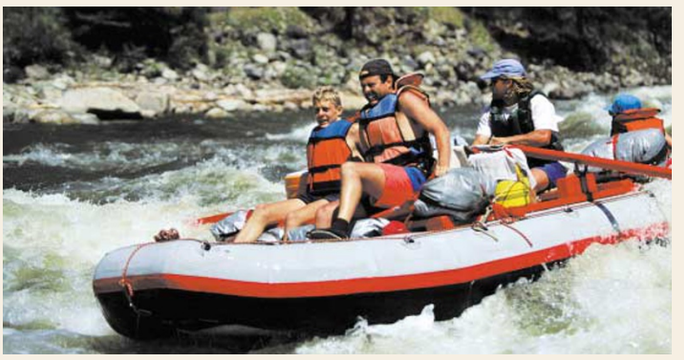
As beclin 1 participates in autophagy, Yue *et al.* explored the question of whether its interaction with nPIST and GluRδ2 modulates its role in the death process. They found that co-expression of nPIST and beclin 1 increased the number of autophagic cells compared with that observed when beclin 1 was expressed alone. Strikingly, this increase was found to be significantly larger if nPIST lacked the domain that interacts with GluRδ2. Similarly, co-expression of beclin 1 with the lurcher mutant, but not with wild-type GluRδ2, increased the number of autophagic cells. Last, the authors found that

CELL BIOLOGY OF THE NEURON

A raft of possibilities

Neurotransmission can be regulated at several levels, including the rate of neurotransmitter release, the availability of receptors on the postsynaptic membrane and the activities of downstream signalling pathways. In a paper published in the *Journal of Neuroscience*, Delling *et al.* now show that an adhesion molecule can regulate the lipid-raft-dependent trafficking of an ion channel, and this might provide a new mechanism for controlling synaptic transmission.

It was previously shown that, in mice deficient in the neural cell-adhesion molecule NCAM, the serotonin 5-HT_{1A} receptor becomes more responsive to certain agonists than that of wild-type littermates. However, there was no evidence that NCAM affects the expression or function of the receptor itself, so Delling *et al.* turned their attention to another component of the signalling pathway.



The signalling activity of the 5-HT_{1A} receptor is mediated through the inwardly rectifying potassium channel Kir3, and the authors showed that Kir3 currents were increased in the absence of NCAM. However, NCAM did not affect the overall expression levels of Kir3, nor did it seem to alter the conductance of individual channels. By transfecting NCAM and Kir3 RNA into *Xenopus* oocytes and neurons, Delling *et al.* showed that in the presence of NCAM, fewer of the Kir3 channels became localized to the cell membrane, indicating that this adhesion molecule blocks the transport of these channels to the cell surface.

So, how does NCAM prevent the channel from reaching its destination? An important clue came from the observation that both NCAM and Kir3 are associated with lipid rafts — cholesterol-rich lipid domains that are used to transport proteins around the cell and to organize signalling complexes on the membrane. NCAM can be modified by the lipid palmitate, and only the palmitoylated

dying Purkinje cells in lurcher mice showed the morphological features of autophagy.

So, autophagy participates in neuronal death in lurcher mice, although we still need to discover how the mutation in GluRδ2 triggers the process. More importantly, as glutamate excitotoxicity is though to account for cell death in several neurological conditions, we need to determine whether similar cascades are associated with other glutamate receptors, and whether these pathways are the real culprits in such disorders. The data of Yue *et al*. broaden the functional repertoire of what are commonly regarded as ionotropic receptors, to encompass signalling pathways that involve protein–protein interactions.

Juan Carlos López

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form can associate with lipid rafts. Delling *et al.* found that if they removed the palmitoylation site from the NCAM molecule, the delivery of Kir3 channel subunits to the membrane was increased, indicating that the association of NCAM with lipid rafts somehow prevents these rafts from delivering Kir3 channels to the cell surface.

The precise mechanism by which NCAM regulates Kir3 trafficking is not yet clear, and this will be an important question to address in the future. It will also be interesting to find out whether the trafficking of other signalling molecules is regulated in the same way, opening up a whole raft of possibilities for future study.

Heather Wood

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ION CHANNELS

ASIC-nal integrator

Acid-sensing ion channels (ASICs) are members of the degenerin/epithelial Na^+ channel (DEG/ENaC) family. ASICs are expressed throughout the brain, but their function remains poorly understood. As some members of the DEG/ENaC family are mechanosensors, ASICs are also thought to open in response to mechanical stimuli. But, as their name indicates, these channels are primarily activated by a decrease in pH. A nagging question about the physiological role of ASICs arises from the fact that many of them require marked and abrupt changes in pH to open. As such changes might be uncommon in the nervous system, it is conceivable that there are other factors that affect ASIC function. Now, reporting in *The Journal of Physiology*, Allen and Attwell show that ASICs might act as signal integrators, responding to a series of changes that ensue during episodes of ischaemia.

During ischaemia, the extracellular concentration of potassium rises, causing cell swelling within minutes. Simultaneously, the intracellular levels of calcium increase, leading to the release of molecules such as arachidonic acid. Last, the anaerobic conditions that result from an ischaemic episode lead to the production of lactate and other metabolites. Allen and Attwell tested whether these factors had any effect on ASIC-mediated currents in cerebellar Purkinje cells, and found that all of them potentiated the ionic influx through the channels. They first established that extracellular acidification elicited an ASIC-mediated current, which had two separate components: a fast, transient peak and, in a subset of cells, a persistent current of smaller amplitude. Membrane stretching elicited by a hypotonic solution, arachidonic acid and lactate all independently potentiated the peak ASIC-mediated current. In addition, arachidonic acid also increased the number of cells that showed a persistent ASIC current.

The data of Allen and Attwell provide good evidence that, as had been proposed, ASICs are gated by mechanical stimuli. And importantly, they point to these channels as possible integrators of some of the changes that take place in parallel during ischaemia, and might therefore be relevant to the concomitant neuronal death. In fact, this integrative capability might be particularly significant, because the decline in pH that accompanies an ischaemic episode might take several minutes to develop. It will be important to investigate the potential of ASIC channels as drug targets in ischaemia, and it will also be interesting to explore whether the signal-integration properties of ASICs are central to their role under physiological conditions.

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NEURODEGENERATIVE DISORDERS

Netting the aggregate

Although the jury is still out on whether the insoluble deposits that characterize many neurodegenerative diseases are causative or symptomatic, the search to find inhibitors of protein aggregation in such diseases seems to be one of the few possible routes to much-needed therapies. In a recent paper, Erich Wanker and colleagues have stepped-up the pace of the search by introducing a simple method for high-throughput screening of compounds that block the self-assembly of polyglutamine-containing huntingtin aggregates, the pathological hallmark of Huntington's disease (HD).

HD, and the formation of aggregates, results when a threshold number of glutamine residues (>37) are present in the huntingtin protein. The new screening process relies on the fact that aggregated huntingtin is retained by cellulose-acetate membranes, whereas unaggregated huntingtin is not. After incubating polyglutamine-containing huntingtin with potential inhibitor compounds in a 384-well format, the reaction mixtures were filtered through cellulose acetate and captured aggregates were revealed by immunoblotting. Testing a Merck compound library of ~184,000 molecules exposed five groups of structurally similar compounds that reduced the level of aggregation.

The authors reveal the identity of one of the compound groups, which are benzothiazoles that are closely related to Riluzole, a compound that is already used to treat amyotrophic lateral sclerosis. But the most potent *in vitro* inhibitors were shown to be toxic in a cell-based assay of aggregation inhibition, highlighting the difficulty in translating *in vitro* screening results into therapy.

Adam Smith,
Editor, Nature Reviews Drug Discovery

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