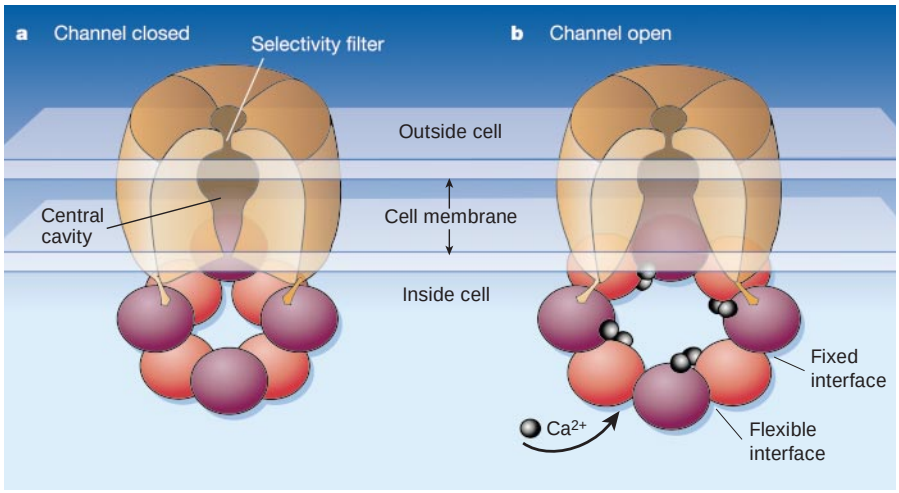

Figure 1 **Schematic model for the gating and opening of a bacterial Ca^{2+}-gated K^+ channel, based on the new papers by MacKinnon and colleagues[1,2].** a, **The closed conformation**; b, **the open conformation. Three of the four subunits of a K^+ channel are shown in brown. The purple and red circles represent the eight RCK domains, which, after binding Ca^{2+}, are thought to reorientate with respect to each other, causing changes in the pore in the centre of the channel.**

pore, including the selectivity filter, is very similar in the two structures. But in the closed KcsA pore the helices of the 'teepee' are nearly straight, whereas they are bent and splayed open in the open MthK pore — and the separate identity of the central cavity is essentially lost.

The hinge of the helices occurs at a particularly provocative position surprisingly deep within the pore, at a glycine amino acid close to the selectivity filter. This makes perfect sense, given the predicted consequences of Ca^{2+} binding: the reorganization of the gating ring exerts an outward, radial force that focuses at the glycine, taking advantage of the flexibility endowed by this amino acid and causing the bend. Sequence comparisons[2] of the pore-lining inner helices from a wide array of K^+-selective channels reveal glycine at an analogous position and an alanine strategically positioned five amino acids carboxy-terminal to the glycine, suggesting that the gating mechanism is conserved across many different channels. The combination of a wide inner cavity and a narrow selectivity filter effectively focuses the membrane to the length of the selectivity filter, some 12 Å, probably explaining the high conduction rates of K^+ channels.

The potential diversity and intriguing similarities of gating mechanisms can be highlighted by comparing MthK with the structure[7] of the ligand-binding domain from a mammalian Ca^{2+}-activated K^+ channel (the SK channel) without the associated pore. In the SK channel, a ligand-binding domain that is unrelated to the RCK domain yet is similarly positioned just beneath the membrane, retains bound calmodulin — a protein that serves as the Ca^{2+}-binding unit. A conformational change after Ca^{2+} binding, involving dimerization of the ligand-binding domain, apparently exerts a force on the attached inner helices and opens the pore[8].

So both channels apparently use a chemomechanical mechanism[7] to couple Ca^{2+} binding to conformational rearrangements that open the pore. Future studies should reveal whether SK channels control their pores according to the model proposed for MthK; this seems plausible, as the mammalian SK channels retain the strategic glycine–alanine motif. Interestingly, in both of these structures[1,7], the 17-amino-acid stretch that links the pore domain with the Ca^{2+}-bound ligand-binding domain was not resolved. This stretch may be the focus for the mechanical force produced by Ca^{2+} binding. Structures of ligand-gated channels that resolve this important linker may provide yet more surprising mechanistic insights. ■

Maria Schumacher is in the Department of Biochemistry and Molecular Biology, and John P. Adelman is at the Vollum Institute, Oregon Health and Sciences University, Portland, Oregon 97201, USA.
e-mail: adelman@ohsu.edu

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Neurobiology

Model hearing

George D. Pollak

For the past 50 years a particular model of how animals locate the source of sounds has driven much of the research on auditory systems. It now seems, however, that this model might not apply to mammals.

Our ability to pinpoint the source of the sounds we hear is quite remarkable, but how do we do it? In general terms, the answer has been known since the time of Lord Rayleigh[1]: the localization of low-frequency sounds relies on a neural computation based on interaural time disparities (ITDs) — differences in the time it takes for a sound to reach each ear. Incredibly, we can detect ITDs of only a few microseconds, allowing us to distinguish between sounds separated by only a few degrees in space[2].

In 1948 Lloyd Jeffress[3] proposed a model that explains how the auditory nervous system processes ITDs and how it represents the particular ITD that is received at the ears. The model is charming in its simplicity and elegance, and has driven much of the research on vertebrate auditory systems for the past 50 years. But Brand and colleagues[4] (page 543 of this issue) now provide evidence for a very different model. They show that the timing of neuronal inhibition — a feature not incorporated in the Jeffress model — shapes ITD processing and representation in previously unsuspected ways.

The Jeffress model for the processing and representation of ITDs has enormous appeal because it incorporates neural processes and structure to account for a behaviour — sound localization. Jeffress envisaged arrays of binaurally innervated neurons, with the neurons in each array presumably all tuned to the same frequency. Each neuron receives an excitatory input from one ear via axons (projections) of a particular length, and an input from the other ear via axons of a slightly different length. The difference in axon lengths creates a delay line, and thus a difference in the times at which action potentials from the two ears arrive at the binaural neuron. This time difference compensates for the ITD between the ears.

The central idea of the Jeffress model is that each neuron fires maximally only when action potentials from the two ears are coincident, arriving at the binaural neuron at the same time. As the delay lines are different for

each neuron, a sound from a particular location, which generates a particular ITD, will produce coincident inputs in only one neuron (or a subset of neurons); all other neurons will receive non-coincident inputs and fire weakly. Changing the location of the sound, and hence the ITD, results in coincidence at a different neuron, and thus at a different place in the array. In this way, the ITD received is encoded by the place in the array at which neurons fire maximally. This arrangement is reiterated for each frequency.

So, for example, a sound emanating from directly ahead will generate an ITD of 0 μs, and coincidence will occur only at those auditory neurons with equal axon lengths. Neurons in each frequency array that are 'tuned' to 0 μs will fire maximally, and all other neurons will fire weakly. In this way, a complex sound originating directly in front of the animal will evoke maximal activity at one place across frequency arrays.

These features appear in the first brain region innervated by the two ears: the medial superior olive (MSO) in mammals and the nucleus laminaris in reptiles and birds. As early as 1953, Stotler[5] reported a striking binaural innervation of MSO neurons. Subsequent neurophysiological studies all showed that these neurons respond to the coincidence of excitatory inputs and are exquisitely sensitive to ITDs in the microsecond range — properties consistent with the Jeffress model[6]. Even more compelling are studies of the nucleus laminaris in birds. There, the Jeffress-type delay lines have been demonstrated anatomically[7], and the place coding of ITDs, resulting from coincidence of excitatory inputs, has been shown with physiological recordings[8–10].

But Brand *et al.*[4] now provide evidence that the MSO in mammals might not work as previously supposed. The authors recorded the electrical activity of MSO neurons in gerbils, animals that are known to localize low-frequency sounds by means of ITDs, and confirmed that each neuron fires maximally at a particular ITD. Yet — and here's the rub — the peak firing occurred at long ITDs that gerbils almost never experience, because their headwidths are too small to generate them. So it is difficult to imagine that ITDs are indeed represented by the place code envisaged by Jeffress.

Brand *et al.* also report that the ITDs that produce maximal firing are closely correlated with the frequency to which each neuron is tuned. Neurons that fire maximally at relatively small ITDs are almost always tuned to higher-frequency sounds, whereas neurons that fire maximally at progressively longer ITDs 'prefer' progressively lower frequencies. So the peak firings generated by a particular ITD are not represented equally in each frequency array of the MSO, as predicted in a Jeffress-like arrangement. Instead, each frequency array responds to a small range of ITDs over which the neuronal firing rate changes markedly.

This leads Brand *et al.* to suggest that, in mammals, the location of a sound is encoded not by the place of maximal firing but rather by the activity pattern across the entire population of auditory neurons, with these neurons changing their firing rates as ITDs change. In their model, high frequencies, which generate the steepest changes in firing rate with ITD, are scaled to peak at small ITDs so that the steep rate changes occur within the biologically relevant ITD range. Conversely, low frequencies, which generate the shallowest rate changes with ITD, are scaled to peak at longer ITDs so that the largest changes in firing also occur within the biologically relevant ITD range.

But the most surprising result occurred after Brand *et al.* blocked inhibitory inputs to MSO neurons. They found that all neurons tested, regardless of their usual behaviour, now fired maximally at ITDs of and around 0 μs. Although the authors blocked inhibition in only a few MSO neurons, their results suggest that delay lines of excitatory inputs are not arranged to produce a range of ITD sensitivities, as Jeffress proposed. Rather, the implication is that, regardless of their arrangement, all neurons fire maximally at ITDs of 0 μs. Inhibition, or more specifically its timing relative to excitation, then sculpts a variety of ITD sensitivities out of the common 0-μs sensitivity produced by the excitatory inputs.

This work raises several questions. Why do mammals and birds have different mechanisms for localizing sounds? And what structural features underlie the inhibitory delay lines suggested by Brand *et al.*? Finally, gerbils are small mammals with small headwidths, and their peak neuronal firing occurred at ITDs that their headwidths could not generate. But what about larger mammals, whose headwidths generate much longer ITDs — does inhibition have a role to play here, too? All in all, the study by Brand *et al.* will no doubt generate considerable discussion about mechanisms that many had thought were already solved. ■

George D. Pollak is in the Department of Neurobiology, University of Texas, Austin, Texas 78712, USA.
e-mail: gpollak@mail.utexas.edu

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Daedalus

Spatial audio

In electron spin resonance (ESR), a chemical sample is placed in a strong magnetic field and irradiated with microwaves. Unpaired electrons in the sample reveal themselves by resonating. Daedalus has been musing on interstellar space, and its content of hydrogen atoms. Each has an unpaired electron (indeed, it is the only one it has). In the low magnetic field of space, each electron should resonate feebly at some audio frequency. Yet the total signal might be quite strong: there are cubic light-years of this specimen. Indeed, the distribution of monatomic hydrogen, and the range and intensity of the interstellar magnetic field itself, are all hot astronomical topics. Daedalus reckons that audio frequencies from space are well worth looking for.

An audio signal would have a very long wavelength — 200 km or thereabouts. A directional parabolic aerial, which must be many wavelengths across, could never be made big enough. Even a conventionally resonant quarter-wave aerial of 50 km would be hard to build. But Daedalus recalls that power-lines and telegraph cables, thousands of kilometres long, already span the globe. Furthermore they are liable to dangerous surges when solar magnetic effects induce big voltages in them. This astrophysical phenomenon suggests to him that a careful search should be made on these conductors, looking for another astrophysical effect: small but detectable audio frequencies from space.

Of course 50 Hz and 60 Hz, the main human power frequencies, will contribute hugely, and will have to be well filtered out. These, however, will have their own human rhythm, caused by the known changing load. The audio spectrum to be studied is wide, too. Furthermore, the system as a whole will be steadily scanned in longitude by the rotation of the Earth, and in latitude by choosing the right conductors to listen to. Circumpolar ones, for example, should discriminate rather well against equatorial signals or ones from the wrong hemisphere.

Here, says Daedalus, is a new way of testing the theory of 'steady-state continuous creation'. It holds that monatomic hydrogen is appearing steadily throughout space, at just the rate needed to compensate for spatial expansion. The Universe has no beginning and no end. If the Earth is indeed receiving a steady ESR hydrogen signal from every point in space, the implications would be cosmologically profound indeed. David Jones