bands increased in the medial-to-lateral axis (Fig. 1). No changes in band number occurred between E17 to P0 and P1 to P4. This developmental pausing could indicate staggering of an underlying inductive signal or the presence of multiple regulatory processes that are separated in time.

When sharp, segmental boundaries in gene expression exist during early development, such as in rhombomeres, genes encoding nuclear proteins frequently delineate these segments or regions (*14*). Indeed, the presumptive T cell oncogene, rhombotin, not only has an early rhombomeric expression but also reveals a banding pattern in neonatal cerebellum that may be complementary to L7βGal (*15*). Afferent projections to cerebellum also are distributed in an anterior-to-posterior, bandlike organization (*16*). Thus, the cell-autonomous mechanisms that establish the Purkinje cell map delineated by L7 expression may be the same as those that guide the establishment of functional circuitry in cerebellum.

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Interaural Phase Coding in Auditory Midbrain: Influence of Dynamic Stimulus Features

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A laterally located sound source stimulates the two ears at slightly different times, generating interaural phase disparities (IPDs) that are used for sound localization. Under natural conditions, such interaural cues are likely to be constantly changing, or dynamic. In the inferior colliculus of gerbils and cats, the nonlinearities in the coding of dynamic interaural phase cues are demonstrated. Responses to ecologically realistic phase cues are more reflective of the change of IPD than of the absolute IPDs over which that change occurs. This observation is inconsistent with the established view that directional information is coded in terms of absolute IPD.

IPD IS AN IMPORTANT SOURCE OF SPATIAL information in audition. Because an observer's head is normally free to move and many sound sources are mobile, most naturally occurring IPDs are likely to be dynamic. Temporal variation of IPD can be viewed either as a source of information or confusion for the auditory system. The former view is suggested by psychophysical data demonstrating that human subjects can accurately discriminate velocity (*1*) and direction (*2*) of moving sounds; the latter view by demonstrations that spatial acuity of the human auditory system is best for static sound sources and decreases as a function of sound source velocity (*3, 4*). Physiological studies have emphasized the similarity of responses to static and dynamic IPD stimuli for the majority of IPD-sensitive neurons throughout the ascending auditory pathway (*5–8*). We now report consistent differences between responses of inferior colliculus (IC) neurons to static and dynamic IPDs in both gerbils (*Meriones unguiculatus*) and cats. By varying the depth of interaural phase modulation (IPM) to approximate the changes of IPD generated by sound-source motion more closely than was possible before, we demonstrate strong influences of dynamic IPD on the responses of the majority of phase-sensitive units (neurons). These neuronal response properties may underlie the sensitivity of the auditory system to dynamic IPD stimuli.

For sounds in the range of tonal frequencies to which neurons are phase sensitive, the largest possible change in IPD, corresponding to motion of a sound source from one side of the head to the other, is less than 360° in mammals. Furthermore, the IPD modulations associated with naturally occurring sound-source motion are usually smaller than the maximum that is possible. The current understanding of neural responses to dynamic interaural phase cues derives from use of the binaural beat stimulus, which produces a continuous, unidirectional change of interaural phase through 360°. For this study, we developed an alternative binaural stimulus that permits the generation of more ecologically realistic IPDs. A phase-modulated, tonal signal is presented at one ear, while the other ear receives an unmodulated reference tone, identical in frequency and sound-pressure level (SPL) to the carrier of the modulated signal. By adjusting parameters of the modulation waveform, including its depth (Fig. 1), we can generate IPM approximating various aspects of simulated auditory motion.

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Responses to static and dynamic IPD stimuli were compared for 145 single units in 19 gerbils and 36 units in two cats. All recordings were from the central nucleus of the inferior colliculus of anesthetized animals (*9*). Sensitivity to IPD is evident in the entrainment of neural discharges to IPM (Fig. 1), which reflects a binaural rather than a monaural process (*10*). Neurons respond almost identically to 360° IPM and the equivalent binaural beat (Fig. 2A). Consistent with other findings (7), the shapes of IPD-discharge profiles are generally similar for static and dynamic stimuli. Nevertheless, dynamic stimuli typically elicit greater proportional modulations of discharge and a greater range of absolute firing rates (Fig. 2, B through D), indicating that IPD-sensitive units are more responsive to dynamic than to static stimuli. Some units, particularly in cats, exhibited adaptation in response to static stimuli of long duration (*11*), and this undoubtedly contributes to the difference in maximum discharge rates obtained under the two stimulus conditions. However, dynamically elicited responses are typically characterized not only by greater peak discharge rates but also by sharper peaks and broader troughs: effects that could not arise from adaptation. The sharper tuning exhibited under dynamic stimulus conditions is illustrated for a large sample of neurons in Fig. 3.

The differences between responses to static and dynamic IPDs may reflect an alteration of the balance between the excitatory and inhibitory influences that determine IPD selectivity of units in the IC (*12*). Thus, reducing the depth of IPM to ecologically plausible values should further alter the balance of these opposing influences. One might expect a reduced-depth IPM to elicit a response biased toward inhibition, if centered on the response minimum, and towards excitation, if centered on the maximum. Alternatively, if responses depend on absolute IPD alone, reducing the depth of IPM should have little effect on the response over the range of conserved IPDs. In fact, the responses to IPM of reduced depth do not conform to either expectation (Fig. 4A).

Figure 4 shows responses of two units to phase sweeps of varying depths, demonstrating that the same IPD may be associated with drastically different evoked discharge rates depending on the context of stimulation within which it occurs. The nonlinear relation between absolute IPD and firing rate under different dynamic stimulus conditions illustrated by these two examples is a general feature of the responses of IPD-sensitive units in both species. Of 117 units studied in detail with reduced-depth modulation stimuli, 78 (64 gerbil, 14 cat) exhibited strongly nonlinear behavior, 4 (3 gerbil, 1 cat) displayed clearly linear behavior, and 35 exhibited intermediate properties. These observations are inconsistent with the notion that responses are primarily determined by absolute IPD and instead demonstrate a profound influence of dynamic stimulus features. For many units the dynamic influence becomes more apparent as the depth of modulation is reduced. For example, whereas IPD tuning of unit 01M001.013 was comparable for static and full-depth dynam-

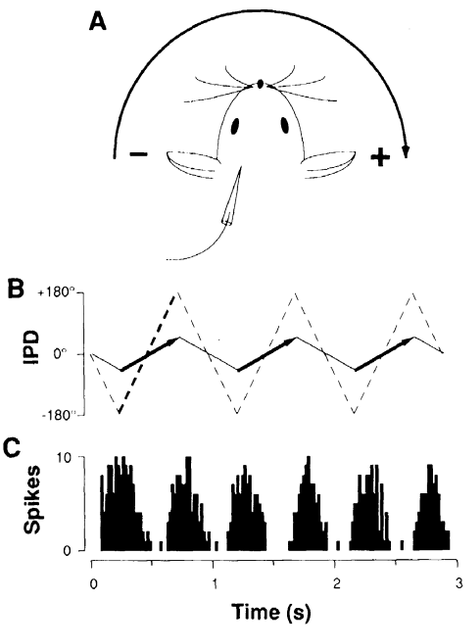
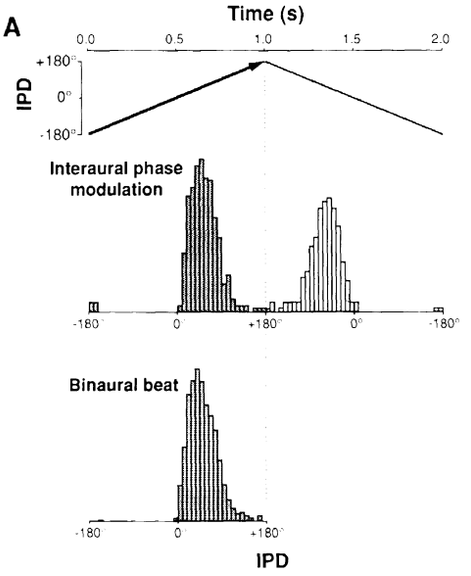


Fig. 1. The changing IPD produced by acoustic motion around an observer's head (**A**) can be approximated by IPM (**B**). Dashed trace in (B) illustrates triangular IPM to ±180° depth. Each half-cycle (dark line) is equivalent to one binaural beat cycle, both producing linear modulation through 360° of IPD. Segments of an IPM stimulus of reduced depth (arrows) simulate the dynamic IPD cue generated by sound-source motion depicted in (A). (**C**) Peristimulus histogram (PSTH) from gerbil unit 00M032.002 demonstrates response entrainment to the shallow-depth stimulus depicted in (B). Positive IPD values correspond to the hemifield contralateral to the recording site. Stimulus: 2000-Hz carrier at 10-dB SPL (referenced to 20 μPa), ±45° depth, 1.0-Hz modulation. In this and other figures, the modulation waveform is triangular (*10*) and was applied to the left ear.



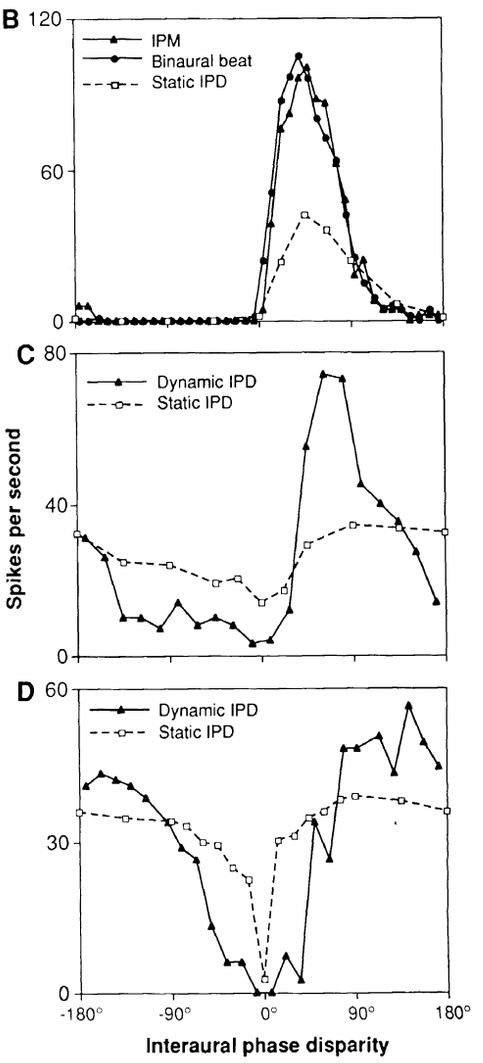


Fig. 2. Period histograms and graphs demonstrating the relation of neuronal responses to dynamic IPD. Each spike is referenced to the onset of the current stimulus period, effectively folding the PSTH time base into one stimulus cycle. (**A**) Responses of cat unit 01M001.017 to a 0.5-Hz IPM of full depth. One half-cycle of modulation (shaded bars) is equivalent to a 1.0-Hz binaural beat (that is, IPD changes at the same rate over the same range). (**B**) The profiles of the dynamically elicited responses in (A) are compared with the tuning function derived statically. The dynamic peak rates exceed the static peak rate by more than 100%. (**C**) Gerbil unit 00M042.007. (**D**) Gerbil unit 00M046.001. Stimuli in (A) and (B): 40 dB SPL. IPM: 1150-Hz carrier, phase modulated to ±180° depth, 0.5 Hz, four trials for 10 s each. Binaural beat: 1150.5 Hz (left ear) and 1149.5 Hz (right ear), four trials for 10 s each. Static: 1150-Hz tone, two trials for 10 s each per stimulus. Stimuli in (C): 800 Hz, 30 dB SPL, five trials for 8 s each. Dynamic: ±180° depth, 0.5 Hz. Stimuli in (D): 4000 Hz, 0 dB SPL, four trials for 10 s each. Dynamic: ±180° depth, 1.0 Hz.

ic stimuli (Fig. 3), responses to stimuli of reduced depth were strongly nonlinear (Fig. 4B).

How is it possible that different changes of firing rate are elicited from the same unit by essentially the same stimulus (for example, a sweep from −15° to +15°) occurring in different contexts? Linear summation of excitatory and inhibitory influences associated with each successively encountered interaural phase angle should produce responses to small sweeps of IPD that are indistinguishable from equivalent segments of the responses to larger sweeps. Instead, responses to dynamic IPD apparently reflect temporal summation of influences associated with the different angles through which interaural phase is swept. According to this interpretation, the difference between responses at the same phase angle within sweeps of different depths is attributable to differences in the stimuli preceding that phase angle. Consequently, instantaneous probability of discharge reflects not only current stimulus conditions but also the recent history of stimulation.

Established theory holds that IPDs are encoded within the superior olivary complex by instantaneous linear summation of inputs arising from the two ears (*6, 13–15*). According to this "coincidence detection" model, the probability of discharge is greatest when inputs stimulate the coincidence detector cell simultaneously, thus conferring tuning to a limited range of IPD. This IPD tuning is faithfully relayed to higher levels of the auditory system, including the inferior colliculus and auditory cortex (*5, 7, 12*). The critical directional information encoded according to this scheme is absolute IPD. Responses to static IPD observed in this study are compatible with this model. However, the fact that dynamically elicited responses reflect the recent history of stimulation is difficult to reconcile with a simple coincidence detection model. Moreover, the nonlinearity of responses expressed under dynamic conditions would degrade a code for spatial position based on absolute IPD because a given IPD can elicit different discharge rates in different stimulus contexts. Dynamically elicited responses are more reflective of the change of IPD than of the absolute IPDs over which that change occurs. This finding suggests that, under dynamic stimulus conditions, the auditory system makes use of relative spatial cues.

What is the significance of these dynamically determined response properties for the encoding of ecologically realistic IPDs? The carrier frequency selected for stimulation of unit 01M001.013 (Fig. 4B) was 850 Hz. At that frequency for a cat, the maximum IPD expected in the open environment would be approximately ±135° (*16*). Naturally occurring motion would therefore produce changes of IPD smaller than ±135°. Responses to full-depth IPM or static IPDs alone suggest that this unit might most sensitively encode small changes of IPD through the periphery of its receptive field (Fig. 4B). Conversely, a modulation through 90° of IPD centered on the midline, corresponding to the change of IPD expected for a sound source traveling through a horizontal arc of 60°, might produce little modulation of the neuron's discharge. The actual response of the unit to such a stimulus, however, consisted of a modulation from near-minimal to near-maximal firing rates. These response properties thus enable the unit to encode sensitively the relatively small changes of IPD associated with ecologically plausible sound-source motions. Physiological studies have generally concluded that units capable of encoding motion-specific stimulus features, such as direction (*7, 8, 17*) and rate (*7, 8*) of change of interaural time differences, are rare in the inferior colliculus. Nevertheless, our study reveals that sensitivity to relative change of IPD is widespread. This conclusion is consistent with psychophysical data suggesting that the auditory system is sensitive to relative change of positional cues (*4, 18*). Special sensitivity to relative change of IPD might be useful for localization of sound sources by an active listener in a constantly changing environment.

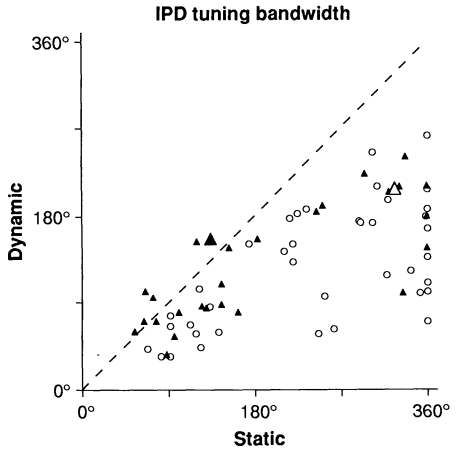


Fig. 3. An illustration of the typically sharper tuning to IPD elicited under dynamic, as opposed to static, stimulus conditions. Excitatory bandwidth was measured in degrees at 50% of peak firing rate. Where rates modulated less than 50% of maximum, the bandwidth was considered to be 360°. Data are shown for all units (21 cat, 45 gerbil) studied both with static stimuli and with dynamic stimuli presented at either 360°/s (triangles) or 720°/s (circles). Units examined in Fig. 4, A and B, are indicated by large open and closed triangles, respectively. Dashed line, values at which IPD tuning is equivalent with dynamic and static stimuli.

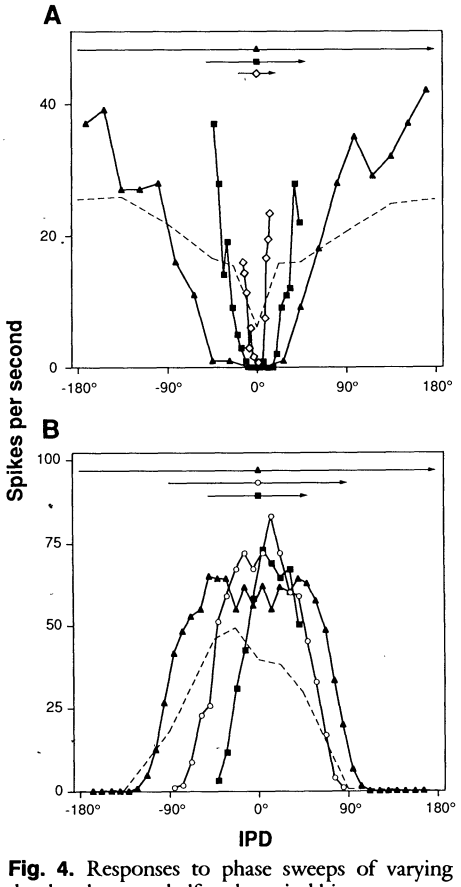


Fig. 4. Responses to phase sweeps of varying depths, shown as half-cycle period histogram profiles. We maintained a constant rate of change of IPD (360°/s). (**A**) For gerbil unit 00M042.002, the phase sweeps are centered about the minimum of the static-delay curve (dashed line). Relative to the static condition, a dynamic stimulus of ±180° depth (triangles) elicits a broader trough and larger range of discharge rates. Stimuli of shallower modulation depth elicit discontiguous response profiles that overlap only at 0°. (**B**) For cat unit 01M001.013, a symmetrically opposite response to reduced-depth modulation occurs when phase sweeps are centered near the maximum of the static delay curve (dashed line). Stimuli in (A): 3500 Hz, 10 dB SPL. Dynamic depth by rate combinations of ±180° by 0.5 Hz (triangles), ±45° by 2 Hz (squares), and ±15° by 6 Hz (open diamonds), five trials for 8 s per stimulus. Static: four trials for 10 s per stimulus. Stimuli in (B): 850 Hz, 10 dB SPL, four trials for 10 s each stimulus. Dynamic depth by rate combinations of ±180° by 0.5 Hz (triangles), ±90° by 1 Hz (open circles), and ±45° by 2 Hz (squares).

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9. Gerbils were anesthetized with 60 mg of pentobarbital per kilogram of body mass, supplemented with ketamine (~25 mg/kg per hour). Cats were sedated

with ketamine (30 mg/kg) and maintained areflexic with pentobarbital administered intravenously (~20.0 mg/kg the first hour, then 2 to 4 mg/kg per hour thereafter). Digitally synthesized sounds were presented dichotically by means of sealed, calibrated delivery systems in a sound-attenuating chamber. Each action potential and various temporal features of the stimulus were detected with 1-μs resolution. Recording sites were verified histologically.
10. No units studied entrained to monaural phase modulation in absence of the reference signal. Identical responses were obtained when the signals at the two ears were switched, if the direction of modulation was reversed. Responses similar to those obtained with triangular modulation were obtained with sinusoidal modulation.
11. Cat neurons tuned to frequencies above 2.0 kHz typically show pronounced adaptation to static IPD stimuli with long durations. Nonadapting units commonly respond most sensitively to frequencies below 2 kHz. Similar adaptation was rarely seen at any frequency in the gerbil.
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The Anion Paradox in Sodium Taste Reception: Resolution by Voltage-Clamp Studies

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Sodium salts are potent taste stimuli, but their effectiveness is markedly dependent on the anion, with chloride yielding the greatest response. The cellular mechanisms that mediate this phenomenon are not known. This "anion paradox" has been resolved by considering the field potential that is generated by restricted electrodiffusion of the anion through paracellular shunts between taste-bud cells. Neural responses to sodium chloride, sodium acetate, and sodium gluconate were studied while the field potential was voltage-clamped. Clamping at electronegative values eliminated the anion effect, whereas clamping at electropositive potentials exaggerated it. Thus, field potentials across the lingual epithelium modulate taste reception, indicating that the functional unit of taste reception includes the taste cell and its paracellular microenvironment.

THE PERCEIVED SALTINESS OF SODIUM salts varies significantly with the anion present. For anions other than chloride, saltiness is attenuated or gustatory qualities other than saltiness appear (*1*). Because the anion effect can be seen in recordings from the chorda tympani (CT) nerve of animals, its origin seems to be peripheral (*2*). Neurophysiological investigations (*3*), lingual epithelial ion transport studies (*4*), and patch-clamp recordings from taste-bud cells (*5*) have established that a major Na^+-transducing element is an amiloride-blockable ion channel in the plasma membrane of taste receptor cells. An amiloride-insensitive Na^+ transducer may also exist (*6*). The effects of the anions of salt stimuli are less well understood. Various blockers of Cl^- cotransport (electroneutral anion exchange involving Cl^-) and antibodies against Cl^- channels have no effect on the CT response of the rat to NaCl (*7*). These results suggest that specific cellular Cl^- transport processes are unlikely to be the major cause of the anion effect. The large effect of the anion on the neural response makes this result seem paradoxical. The alternative that anions might affect taste reception through diffusion potentials across shunts between receptor cells has been proposed (*7, 8*), but the hypothesis has not been tested.

We used the technique of Heck *et al.* (*9*) to test whether relative changes in paracellular anion permeability could affect the transepithelial potential across the taste buds and, in turn, the neural response. This method permits either voltage-clamping or current-clamping a macroscopic patch of rat dorsal lingual epithelium while simultaneously monitoring the CT response from the taste fibers innervating the patch (*10*). We used three stimuli: NaCl, sodium acetate (NaAc), and sodium gluconate (NaGlu). Figure 1A shows the change in transepithelial potential across the patch (*11*) evoked by 0.5 M NaCl, NaAc, and NaGlu. NaCl caused an electropositive change in the potential and a decreased resistance relative to the rinse solution (0.03 M NaCl in this case). The CT response, recorded simultaneously, is shown below in Fig. 1A. Changing the salt to NaAc produced a more electropositive potential, a smaller decrease in resistance, and the typically lower neural response. With NaGlu as the stimulus the electropositive potential increased further, the resistance decrease was smallest, and the neural response was the lowest of the three test salts.

This pattern of CT response for the test salts occurred for concentrations from 0.05 to 0.5 M so that NaCl > NaAc > NaGlu (Fig. 1B). The pattern for the transepithelial potential change over the same concentration range (Fig. 1C) was exactly opposite: NaCl < NaAc < NaGlu. Changes with concentration in transepithelial conductance paralleled those of the neural response with the same rank order (not shown). The lingual epithelium transports both Na^+ and Cl^- ions (*4, 12*). Pathways for ion flow are both active and passive, and some evidence indicates that a major passive route is paracellular (*4, 12, 13*). The data in Fig. 1 are consistent with the anion effect on the neural response being mediated through a paracellular shunt. Chloride, the most conductive of the three anions, provides a shunting current that minimizes the electropositive potential created by the transcellular and paracellular transport of Na^+. Once established, the electropositive potential could act as a hyperpolarizing field potential depressing the receptor potential of the taste cell (*7, 8*).

If this hypothesis is correct, then it should be possible to voltage-clamp the field potential so that anion diffusion potentials do not influence the receptor potentials or, therefore, the neural responses. This setup can be achieved by clamping the inside of the lingual epithelium at electronegative potentials. At −90 mV, the neural responses to NaCl, NaAc, and NaGlu did not differ significantly from one another (Fig. 2). The evolution and the direction of the stimulus-evoked currents at negative clamping voltages were similar for all three test salts. These data are consistent with the convergence of the neural response magnitudes and indicate that the major electrical consequences of anion shunting were eliminated.

In contrast, with a clamping voltage of 90 mV the neural responses to NaCl, NaAc, and NaGlu were significantly reduced (Fig. 2). Responses to NaAc and NaGlu were especially inhibited, rising just above baseline. To sustain a clamping voltage of 90 mV with NaCl, an inward current was required because of the high shunt Cl^- conductance. The smaller inward current required to sustain 90 mV in the case of the lower-conductance acetate ion was consistent with this result. Gluconate, the ion with the lowest conductance, provided the poorest shunting so that a small outward clamp-

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