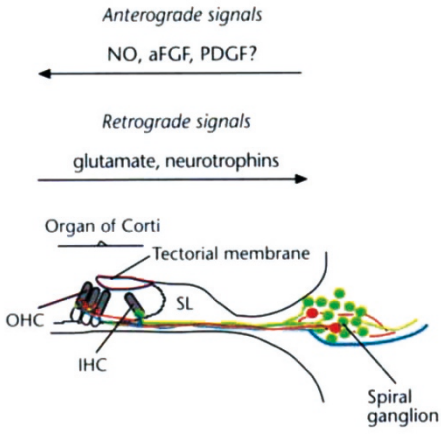

Fig. 2 Schematic representation of the spiral ganglion and its interaction with the outer and inner hair cells of the organ of Corti. Type 1 spiral ganglion neurons (green) innervate inner hair cells and type 2 neurons (red) innervate outer hair cells. Efferent cochlear innervation is indicated in blue. Also indicated are anterograde and retrograde neurotransmitters and trophic factors that mediate communication between hair cells and spiral ganglion neurons. (NO, nitric oxide; aFGF, acidic fibroblast growth factor; PDGF, platelet-derived growth factor; IHC, inner hair cell; OHC, outer hair cell; SL, spiral limbus).

neurons is likely to be counterbalanced by the release of protective trophic factors from these same cells. For example, one potentially important trophic molecule known to be manufactured by spiral ganglia is acidic fibroblast growth factor (aFGF). This anterograde factor is important for the differentiation and maintenance of supporting cells under normal conditions and perhaps also for sensory hair cells, which express FGF receptors following trauma[6,7]. In addition, if PDGF proves to be a crucial maintenance factor for hair cells, aminoglycosides (which are known PDGF antagonists) could interfere with this activity thus contributing to hair cell degeneration[8].

It is clear that trophic signaling in the cochlea is reciprocal: retrograde neurotrophic factors produced by hair cells protect the spiral ganglion neurons and anterograde factors released by spiral ganglia nourish hair cells (Fig. 2). The neurotrophins, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), are produced by hair cells and act on neurons in the cochlea[9,10]. Whereas NT-3 is physiologically crucial for the survival of developing type 1 spiral ganglion neurons innervating inner hair cells, BDNF is required for the survival of type 2 spiral ganglion neurons innervating outer hair cells[11]. In the adult, NT-3 fully prevents aminoglycoside-induced loss of spiral ganglion neurons[12]. In our view, the balance of retrograde and anterograde trophic signaling in the inner ear determines the susceptibility of hair cells and spiral ganglion neurons to damage. Therefore, complete abrogation of aminoglycoside-induced inner ear damage will require blocking the excitotoxic activity of aminoglycosides and restoring the balance of trophic factors in the cochlea.

Regardless of the mechanisms of action of NMDA antagonists and whether the effects on hair cells are direct or not, the fact is that from having no methods for preventing damage to the inner ear a year ago, we now have candidate drugs with protective properties for hair cells and neurons that potentially can prevent hearing loss in human patients.

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Interleukin 1β and fever

Recombinant poxviruses expressing soluble interleukin-1 receptors show that interleukin-1β is the predominant pyrogen during poxvirus infection.

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Fever is an elevation in body temperature (typically 1 to 4 °C) that occurs as a nonspecific response to infection, contributing to host defense and survival through effects on inflammatory and immune responses[1–3]. The search for an endogenous agent that causes a rise in temperature (pyrogen) has been long. Although fever was first described in an Egyptian papyrus 5000 years ago, the biological activity of an endogenous pyrogen was not reported until 1955 (ref. 4).The discovery of the first cytokines offered the promise that the endogenous molecule(s) that caused fever had finally been identified[2]. However, although interleukin-1 (IL-1) α and β, tumor necrosis factor (TNF) α and β, IL-6 and interferons have all been implicated as mediators of fever, it has been difficult to dissect their individual roles because these cytokines are pleiotropic, exhibit redundancy of function and interact with each other at multiple levels[5]. Thus, the all-important question is which cytokine is the endogenous pyrogen? Now, in a recent issue of the *Proceedings of the National Academy of*

Sciences, Alcamí and Smith[3] report the results of an elegant series of experiments using recombinant poxviruses, which show that IL-1β is the long-sought endogenous pyrogen required for fever, at least during poxvirus infection.

The large DNA viruses of the poxvirus family include vaccinia virus, which has been used in a successful vaccination program to eradicate smallpox (caused by the related variola virus). It is well established that different vaccinia strains produce various reactions in the vaccinee, for example, some produce fever whereas others do not. Vaccinia viruses produce a variety of proteins including soluble cytokine receptors that interfere with the host immune response by blockading cytokine activity. In their study Alcamí and Smith analyzed the febrile responses of mice intranasally infected with a number of different vaccinia strains. The Western Reserve (WR) strain has a gene (*B15R*) that encodes an isoform of the IL-1 receptor (vIL-1βR), which binds IL-1β (but not IL-1α or IL-1 receptor antagonist, IL-1ra) with high affinity[6]. Mice intranasally infected with WR strain do not show fever, whereas those exposed to the same strain genetically engineered to lack a functional *B15R* gene exhibited a febrile response. Reinsertion of the gene prevented the febrile response, demonstrating that vIL-1βR is responsible for abrogation of fever. As predicted, IL-1β binding, indicative of vIL-1βR expression, occurred in peripheral tissues (spleen, lungs, plasma) and brains of mice infected with WR wild-type strain but not in animals infected with the strain deficient in *B15R*. Infection with either the wild-type or engineered WR strains resulted in similar virus titers, indicating that effects on temperature were due to the B15R phenotype and were not caused by variations in viral load.

Three other smallpox vaccine strains were also studied: the Tian-Tin strain, which also encodes a soluble receptor for mouse IL-1β, failed to cause fever, whereas the Copenhagen and Tashkent strains, which lack vIL-1βR and are both known to cause high fevers in vaccinated humans, induced a febrile response in mice. Insertion of the *B15R* gene into the Copenhagen genome resulted in a virus that expressed IL-1βR and did not induce fever in exposed animals. In addition, treatment with a neutralizing monoclonal antibody to mouse IL-1β blocked the fever induced by wild-type Copenhagen strain. Even though the variola virus is not available for study, it is known that smallpox was associated with high fever. The *B15R* gene is inactive in variola virus, which does, however, have genes predicted to encode receptors for interferon (IFN) α, β, and γ, and for TNF-α and -β, suggesting that fever deriving from smallpox was mediated by IL-1β and not by IFN or TNF (ref. 3). One possible limitation of the study by Alcamí and Smith[3] is that IL-1β immunoactivity could not be detected in plasma after infection of mice with either the wild-type or engineered WR strain. Nevertheless, given the several lines of evidence presented, it is reasonable to conclude that IL-1β is the endogenous pyrogen that induces fever in poxvirus infection. It is noteworthy that others have shown that IL-1β knockout mice have no fever in response to turpentine injection, which causes localized inflammation and tissue injury[7]. Thus, it seems that IL-1β may indeed be a required endogenous pyrogen in a variety of pathophysiological conditions.

If IL-1β is an endogenous pyrogen, then the next question is "how does this cytokine signal the brain to cause fever?" particularly as cytokines do not readily cross the blood–brain barrier (BBB). Peripheral cytokines can reach the brain by one of four possible routes[8]: (1) they can slowly cross the intact BBB via specific (putative) transport mechanisms; (2) they can enter the brain through regions lacking a BBB; (3) they can transmit a signal to the brain through the vagus nerve; and (4) they may activate brain vasculature causing informational molecules such as nitric oxide[9] and prostaglandins to act on brain parenchyma. When these four mechanisms were first proposed by various groups there was a debate as to which one was "correct"; it now seems that each plays a prominent role depending on the conditions. For example, in mild inflammation, when peripheral cytokines are not present in significant amounts in the circulation, the peripheral cytokine signal to the central nervous system is most likely to be transmitted through the vagus nerve. On the other hand, during systemic inflammation and sepsis, when endothelium is activated and levels of circulating cytokines are high, the vascular route to brain activation becomes more important.

Interestingly, it appears that the signal triggered within the brain by peripheral IL-1β is IL-1β itself[10,11]. We have recently shown[11] that, during systemic inflammation, there is first production of IL-1β peripherally, then induction of IL-1β gene expression in areas of the central nervous system that lack BBB, followed by induction of IL-1β gene expression within brain parenchyma in regions where the BBB is intact, such as the paraventricular nucleus of the hypothalamus. Peripheral IL-1β and brain IL-1β are the same molecule but exert different actions depending on the local conditions.

With the identification of IL-1β as the major endogenous pyrogen in poxvirus infection, Alcamí and Smith, have solved a long-standing puzzle. The next step will be to discover whether IL-1β is the predominant endogenous pyrogen in all inflammatory conditions or whether, in keeping with current thinking regarding the functional redundancy of cytokines, other molecules such as IL-1α, TNF-α, IL-6 and interferons mediate fever under different conditions.

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