Neurobiology

Arachidonic-acid metabolites as second messengers

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INTRACELLULAR second messengers (cyclic nucleotides, calcium, diacylglycerol and inositol polyphosphates) are known to mediate a wide variety of regulatory extracellular signals involved in functions as diverse as cellular growth control and neurotransmission. The report by Piomelli *et al.* on page 38 of this issue[1] provides strong evidence that eicosanoids (arachidonic-acid metabolites) can be added to the list of second messengers. In this article, three groups at Columbia University and the University of Texas show in an elegant series of experiments that an eicosanoid, probably 12-hydroperoxyeicosatetraenoic acid (12-HPETE), acts as a second messenger at a synapse in the marine mollusc *Aplysia californica*. Specifically, this compound is responsible for the inhibitory effects of FMRFamide on 5-HT (serotonin)-induced depolarization of *Aplysia* sensory neurons. (See the discussion[2] in News and Views by Jennifer Altman earlier this year, which contains a schematic diagram of second-messenger regulated neural pathways.)

Arachidonic acid, when released from esterified stores in the cell membrane, gives rise to various biologically active oxidation products, collectively called eicosanoids. Two main enzymatic pathways have been defined: the cyclooxygenase cascade catalyses the production of prostanoids; and the lipoxygenase enzymes synthesize leukotrienes, hydroxyeicosatetraenoic acids (HETEs and HPETEs) and lipoxins[3]. Although the modulatory effects of eicosanoids on cardiovascular, reproductive and immune functions have been the focus of much interest over the past two decades, there has been little information available on any neuronal effects of eicosanoids except for the action of prostanoids on peripheral sensory neurons.

The clues that led Piomelli *et al.*[1] to investigate eicosanoids as potential second messengers originated in their demonstration that histamine application to cerebral ganglia of *Aplysia* evoked arachidonic acid release and breakdown[4]. Histaminergic neurons exert inhibitory effects on abdominal ganglia, and stimulation of these inhibitory neurons also results in arachidonic acid release with a similar spectrum of oxidation products. These observations prompted an analysis of the role of eicosanoids on a better-defined system. 5-HT depolarizes *Aplysia* sensory neurons by indirectly closing a class of potassium channels by a mechanism that involves cyclic AMP-dependent phosphorylation[5]. The report in this issue shows that the neuroactive peptide FMRFamide (Phe-Met-Arg-Phe-NH_2) antagonizes the effect of 5-HT by increasing the probability of the potassium channels remaining open, although this action does not involve the cyclic AMP phosphorylation cascade. Arachidonic acid itself mimics the action of FMRFamide, and inhibitors of lipoygenase, but not of cyclooxygenase activity, block the effect of FMRFamide. With the discovery of the lipoxygenase products 5- and 12-HETE both in synaptosomes and in identified cell bodies, the unstable hydroperoxy-precusors of these compounds were tested for their ability to mimic FMRFamide. 12-HPETE shows such an activity and the authors conclude[1] that this, or a related compound, mediates the action of FMRFamide. Therefore, two second-messenger systems converge to act in opposite ways on a single type of membrane channel.

It may be particularly significant that eicosanoids can pass freely across cell membranes so that they may have a role as both intracellular and extracellular signals. This property also suggests a novel means of trans-synaptic modulation of neuronal activity, which Piomelli *et al.* outline in their article. At some synapses, nerve impulses can lead to a prolonged subsequent increase in the postsynaptic response to a presynaptic input, termed long-term potentiation (LTP)[6,7]. Both pre- and postsynaptic mechanisms have been implicated in LTP, and some of the best evidence shows that a presynaptic modification leading to increased transmitter release can occur during LTP. But at some synapses, the activity of the postsynaptic cell is also important.

Some of the best-studied examples of LTP occur in the hippocampus. Here, pharmacological evidence suggests that activation of postsynaptic NMDA-type glutamate receptors is important for the development of LTP and that polarization of the postsynaptic membrane can influence the establishment of LTP. Experimental evidence, however, shows that there is a presynaptic component of LTP operating at these synapses. Does this result indicate there are two separate loci for LTP or does the postsynaptic activity somehow feed back onto the presynaptic terminal and, if so, how?

Activation of NMDA receptors is known to lead to an increase in calcium influx, and an increase in postsynaptic intracellular calcium levels is necessary for LTP. Although mechanisms such as calcium-mediated phosphorylation of postsynaptic components could explain any postsynaptic locus of LTP, it has not been clear how such changes could modify the properties of the presynaptic terminal. Eicosanoids provide a possible link. The elevated intracellular calcium concentration could promote eicosanoid production through activation of phospholipases; eicosanoids could then diffuse through the membrane to act on or in the presynaptic terminal. Such an action could add to purely presynaptic events that may also involve calcium; perhaps eicosanoids are involved here too.

The demonstration of eicosanoid-mediated second-messenger activity in neurons poses the question of what other cell types use similar mechanisms of signal transduction. Recent experiments demonstrating G-protein control of arachidonic acid release in various cell types are consistent with the notion that receptor-mediated eicosanoid synthesis is a general signal-transduction mechanism subserving a variety of functions. Evidence for eicosanoid stimulation of protein kinase C[8], guanyl cyclase[9] and calcium mobilization[10] from reticular stores suggests that eicosanoids interact with, or mimic, the effects of other second-messenger systems. In support of this idea, a forthcoming article[11] by Schaad, Schoderet and Magistretti demonstrates a role for prostaglandins in mediating the synergism between vasoactive intestinal peptide and noradrenaline in raising cyclic AMP concentrations in the mouse cerebral cortex.

With the use of cyclooxygenase and lipoxygenase inhibitors, the range of systems that use eicosanoids as second messengers should soon be catalogued. It will be considerably more difficult to define the precise site of action of these lipophilic and frequently unstable molecules, and to distinguish truly intracellular actions from effects occurring at the cell membrane. □

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