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Anatomy of Prostaglandin Signals:

An enzymatic step in prostaglandin synthesis plays a key role in neuroinflammation in the mammalian brain

Nephi Stella

Department of Pharmacology, Psychiatry, and Behavioral Sciences, University of Washington, Seattle, WA 98195-7280, USA. nstella@u.washington.edu

Membrane metabolism generates many lipid signals that regulate diverse cellular processes. Although most membrane-metabolizing enzymes are specific to one lipid family, some act on a range of substrates and produce lipid signals with different bioactivities. These multisubstrate enzymes act as nodes that can change the flow of information carried by the lipid signaling network by, for example, boosting the production of one family of lipids while dampening that of another. On page 809 of this issue, Nomura *et al.* (1) show that the enzyme monoacylglycerol lipase (MAGL) (2) is a critical node within the lipid signaling network, coordinating the brain's defense mechanism to neurodegeneration. They also show that inhibiting MAGL prevents neurodegeneration and chronic neuroinflammation in a mouse model of Parkinson's disease, opening a new potential avenue for treating neurodegenerative diseases.

The brain is separated from the rest of the body by the blood-brain barrier, which insulates the central nervous system against toxins as well as peripherally circulating immune cells. It has its own specialized immune system orchestrated by microglia, a type of macrophage that constantly patrols brain parenchyma (3, 4). Microglia become activated in response to pathogens and neuronal damage, rapidly changing into effector cells that initiate and control immune responses. Indeed, microglia are activated by HIV, malaria, tumors, ischemic insults, autoimmune events, and neurodegeneration. However, the phenotype of these activated cells varies depending on the pathology, from releasing toxins that harm adjacent cells, to decreasing the production of toxins and producing immune mediators that protect and repair adjacent cells (5).

The molecular mechanisms that determine the phenotype of activated microglia are controlled by lipid signals. For example, prostaglandins promote (6), whereas endocannabinoids dampen (7), microglia activation. Accordingly, modulating cannabinoid receptor and prostaglandin receptor activity can regulate the duration and outcome of the brain's innate immune responses. Unfortunately, the development of therapies based on synthetic receptor ligands is hampered by the compensatory desensitization or sensitization that follows long-term receptor activation or inactivation, respectively (8). Indeed, the intense search for therapeutic compounds targeting cannabinoid and prostaglandin receptors has yet to produce viable medicines. By contrast, cyclooxygenase 1 (COX1) and COX2 inhibitors, which block prostaglandin synthesis, are well-established treatments that benefit many patients (although a prominent toxicity is gastrointestinal bleeding). By inhibiting the enzymes that produce and inactivate lipid signals, one could control the efficacy of their signaling only where and when active endogenous signaling is already taking place. This is especially important in endocannabinoid signaling because the most abundant endocannabinoid, 2-arachidonoylglycerol (2-AG), activates multiple receptors, including cannabinoid 1 (CB1) and CB2, as well as unidentified G protein-coupled receptors that control fundamental biological processes, such as cell migration and viability (9). The

results of Nomura *et al.* point to a new node of the lipid signaling network, MAGL, as a potential therapeutic target.

Parkinson's disease is associated with the degeneration of dopamine-containing neurons originating from the substantia nigra. The consequential chronic microglia activation and release of harmful molecules exacerbate the degeneration of these neurons (10, 11). Nomura *et al.* show that in a parkinsonian mouse model, oral administration of a compound that inhibits MAGL (JZL184) boosted endocannabinoid signaling and reduced prostaglandin signaling in the brain. These actions, which dampen microglial cell activation, reduced the release of proinflammatory cytokines and prevented degeneration of dopamine-containing neurons. Although it is currently thought that phospholipase A₂ (PLA₂) is the primary enzyme for producing prostaglandins in brain, the authors show that it contributes less to prostaglandin synthesis than the MAGL pathway (see the figure). The finding therefore redefines the textbook view of prostaglandin synthesis in this particular organ.

The study of Nomura *et al.* points to a possible new avenue for developing therapeutics that target the brain's own defense mechanism against neurodegeneration. However, it is not clear why the MAGL inhibitor produced such a predominant effect in the brain, because the enzyme is also expressed by peripheral tissues. In fact, the utility of compounds that target MAGL may expand beyond treatment of chronic inflammation and degeneration. MAGL inhibitors reduce the production of fatty acid signaling lipids that mediate the migration, invasion, and survival of tumor cells, and reduce tumor growth in mouse models of cancer (12). However, it is important to emphasize that chronic and complete MAGL blockade by such compounds causes tolerance, impaired endocannabinoid-dependent synaptic plasticity, and desensitized brain CB1 receptors in mice (13). It will therefore be necessary to identify the signaling events affected by MAGL inhibitors in neurodegeneration, tumor pathogenesis, and tolerance, and determine how the drugs might benefit distinct populations of patients.

The development of unbiased analytical approaches is allowing researchers to rapidly identify how fundamental biological processes are disrupted by pathological conditions—from changes in the genetic information to profiling changes in lipid signaling and entire families of enzymatic activities. These approaches are especially powerful when coupled to classic pharmacology. The findings of Nomura *et al.* suggest that testing the preclinical therapeutic value of MAGL inhibitors could lead to the development of medicines that will benefit patients with neurodegenerative disease by heightening the brain's own protective mechanisms.

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1. . Selective pathways

(**Top**) Arachidonic acid (AA) is primarily produced by the enzyme MAGL (less is generated by PLA₂), which is then converted into proinflammatory prostaglandins (PGs) in the mouse brain. (**Bottom**) In the mouse gut, the AA is produced primarily by PLA₂. However, MAGL is also expressed in gut tissue and produces AA. PI, phosphoinositol; PL, phospholipid; PLC, phospholipase C; CB, cannabinoid; COX, cyclooxygenase; DAG, diacylglycerol; DGL, DAG, DAG lipase.