UCSD chemist describes new approach to onset of premature labor

April 19, 1990

Contact: Yvonne Baskin, (619) 534-0362 For Release After 4:30 PM (EST)

UCSD CHEMIST DESCRIBES NEW APPROACH TO INHIBITING ONSET OF PREMATURE LABOR

BOSTON -- New approaches to blocking a hormone system that mediates everything from the premature onset of labor to asthma, headaches and arthritis pain were presented here Tuesday by a University of California, San Diego biochemist.

The target for controlling this hormone system is an enzyme called phospholipase A2 (PLA2).

"If a safe, effective inhibitor can be found for PLA2, it could open up a whole new class of drugs," said UCSD chemistry professor Edward A. Dennis. Dennis presided at a symposium on PLA2 structure and function during a national meeting of the American Chemical Society in Boston.

The most effective anti-inflammatory drugs now available-- steroids such as cortisol--are believed to act by interfering with the PLA2-initiated pathway, but their side effects are so severe that they are usually reserved for extreme cases.

Dennis' team has developed a cell culture system that allows researchers for the first time to test and study potential PLA2 inhibitors in a laboratory dish. And they have studied a compound--manoalogue, a synthetic derivative of a natural chemical called manoalide found in South Pacific sponges--that inhibits the activity of PLA2 both in isolation and in cell culture.

"We now have an inhibitor that we can use as a model to design other, possibly more effective inhibitors," Dennis said. New novel chemical structures that serve as potent inhibitors of PLA2 were presented by Dennis at the symposium.

"The model also allows us to study the mechanisms by which this system leads to the release of medically important compounds such as prostaglandins and leukotrienes," he noted.

Briefly, the enzyme PLA2 acts on lipids (fats) in the membranes of certain cells to release a fatty acid called arachidonic acid. Another enzyme converts arachidonic acid to prostaglandins, a powerful series of compounds that regulate a whole host of bodily processes, from pain, fever and inflammation to blood pressure, clotting and the onset of labor at the end of pregnancy. Aspirin, ibuprofen And other members of a large class of compounds called nonsteroidal anti-inflammatory drugs (NSAIDs) work by blocking the pathway to prostaglandin formation.

But no effective drugs exist to block two other pathways triggered by PLA2. In one, arachidonic acid is converted into compounds called leukotrienes that are involved in processes ranging from asthma and anaphylactic shock to inflammation. In the second, the action of PLA2 on cell membranes releases a substance called platelet activating factor (PAF).

"PAF is a potent hormone that is implicated in helping in egg implantation and the establishment of pregnancy," Dennis said. "Thus, through several pathways, PLA2 is key to understanding not only what triggers premature labor but what initiates normal labor and delivery.

"It's also a prime new drug target, because controlling PLA2 would open up a way to regulate both the PAF and the leukotriene pathways as well as provide a new control point for the prostaglandin pathway."

The most important sources of PLA2 in pregnancy are probably the amnionic cells in the sac that holds the developing fetus in its bath of amniotic fluid. But these tissues are difficult to study and produce very low amounts of PLA2.

In a search for alternatives, Dennis found that white blood cells called macrophages, which are immunologically activated to fight infections, are very similar to amniotic cells in a number of ways, including their ability to make prostaglandins.

"We cultured macrophages as a potential model for amniotic cells and recently found that we can isolate and purify PLA2 from them," he noted. "Also, we found that manoalogue does inhibit activation of PLA2 in these macrophages. So we have a model system that lets us design better inhibitors and also study the molecular mechanisms involved in regulating PLA2."

Until now, there has been no system available for evaluating PLA2 inhibitors in intact cells. Although the UCSD team's interest is in basic research, other investigators are very interested in using this model to test potential new therapeutic agents.

Dennis' research is supported by grants from the National Institute of Child Health and Human Development, the National Institute of General Medical Sciences and the National Science Foundation.

Recently published articles on the new PLA2 inhibitors include two communications in the February 28 issue of the Journal of the American Chemical Society and a paper in the February 15 issue of The Journal of Biological Chemistry.

(April 24, 1990)