This Weeks Citation Classic®

CC/NUMBER 30
JULY 21, 1991

Bazan N.G. Effects of ischemia and electroconvulsive shock on free fatty acid pool in the brain. *Biochem. Biophys. Acta* 218:1-10, 1970.
(Department of Biochemistry and Clarke Institute of Psychiatry, University of Toronto, Ontario, Canada)

At ischemic onset or after electroconvulsive shock, free arachidonic and docosahexaenoic acids are the predominant endogenous fatty acids accumulated. It is suggested that this reflects phospholipase A_2 activation and that such a mechanism may be important in maintaining excitable membrane properties. (The *SCI*® indicates that this paper has been cited in more than 405 publications.)

Neural Stimulation or Onset of Cerebral Ischemia Activates Phospholipase A_2

Nicolas G. Bazan
LSU Eye Center and Neuroscience Center
Louisiana State University Medical Center School of Medicine
New Orleans, LA 70122-2234

In 1968, in my first laboratory, supported by a grant from the Canadian Medical Research Council, I decided to explore the hypothesis that neural stimulation degrades excitable membrane phospholipids through phospholipase A_2. The basis of the approach was my work as a postdoc in Cliffe D. Joel's lab at Harvard Medical School (1966-1968).

There Cliffe and I developed gradient-thickness thin-layer chromatography to isolate the small free fatty acid fraction from brain tissue in a single step following extraction. We showed that ischemia promotes the accumulation of free fatty acids. Since the identities of the accumulated fatty acids were unknown at the time, we were unable to explain the nature of the phenomeon. In Toronto, I combined gas-liquid chromatography with rapid brain sampling and found that, at the onset of ischemia, free arachidonic and docosahexaenoic acids evolved as the prevalent components of the free fatty acid pool. Was this a postmortem effect of ischemia or was it related to neural activity?

The next experiments were influenced by several non related incidents. At the Clarke Institute of Psychiatry, University of Toronto, I learned about the success of electroconvlusive therapy in treating depression. In addition, ever since early childhood I had been intrigued with epilepsy, having witnessed my aunt suffering a seizure on the street while she was accompanying me to a piano lesson.

During medical school, I realized how little was known about the pathogenesis of this disease. Now, I had the opportunity to look for possible neurochemical alterations during seizures. We know that neurotransmitters are released in the brain during convulsions. I found a transient increase in the pool size of free polyunsaturated fatty acids after convulsions, implying a transient phospholipase A_2 activation. These studies suggested that there is a receptor-mediated release of certain free fatty acids through activation of phospholipase A_2, an event that in turn modulates excitable membrane function.[1] Moreover, increases in cellular calcium ion concentration and lipid peroxidation also may be involved at the onset of irreversible brain damage, particularly during reperfusion after ischemia.[2]

I suspect that the reasons for the frequent citations of this paper are related to the increased interest in the role of arachidonic acid and of its oxygenated metabolites as second messengers of cell signal transduction.[3] This work also was the first demonstration that ischemia in any organ *in-situ* promotes the rapid accumulation of free arachidonic and docosahexaenoic acids. The paper also reported an accumulation of brain diacylglycerols under the conditions of the study.

In retrospect I believe the paper contributed to the understanding of the physiological significance of phospholipase A_2 in excitable membrane function,[1,3] ischemic damage,[2,4] and in epileptic seizures.[5] It was based in part upon this work that I received the Jacob Javits Neuroscience Investigator Award in 1989.

1. **Bazan N.G.** Changes in free fatty acids of brain by drug-induced convulsions, electroshock and anesthesia. *J. Neurochem.* 18:1379-85, 1971 (Cited 105 times.)
2. **Bazan N.G. & Rodriguez de Turco E.B.** Membrane lipids in the pathogenesis of brain edema: phospholipids and arachidonic acid, the earliest membrane components changed at the onset of ischemia. *Advan. Neurol.* 18:197-205, 1980 (Cited 55 times.)
3. **Axelrod J., Burch R.M. & Jelsema C.L.** Receptor mediated activation of phospholipase A_2 via GTP-binding proteins; arachidonic acid and its metabolites as second messengers. *Trends Neurosci.* 110:117-23, 1988. (Cited 80 times.)
4. **Choi D.W.** Cerebral hypoxia: some new approaches and unanswered questions. *J. Neurosci.* 10:2493-504, 1990.
5. **Siesjo B.K., Ingvar M. & Westerberg E.** The influence of bicuculline-induced seizures on free fatty acid concentrations in cerebral cortex, hippocampus, and cerebellum. *J. Neurochem.* 39:796-802, 1982. (Cited 45 times.)

Received November 12, 1990