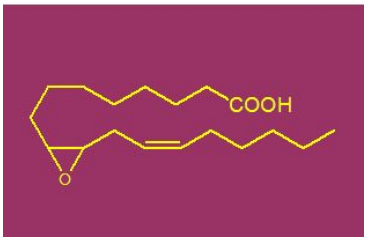
Lipid of the Month: April 2009

Leukotoxin



Ozawa *et al.* in 1986 reported the presence of a toxic linoleate-derived epoxide in lung lavages of rats breathing pure oxygen identified as 9,10-epoxy-12-octadecenoic acid and given the trivial name "leukotoxin" (1). Leukotoxin showed a potent uncoupling effect on mitochondrial respiration and caused relaxation of smooth muscle from guinea pig stomach. Also the regioisomeric 12,13-epoxy-9-octadecenoic acid was detected although this compound showed lower biological activity. These two epoxides had been obtained earlier as chemical monoepoxidation products of linoleic acid (2) or as natural products in plant oils (3), however, their formation in an animal system and their biological activity had apparently been overlooked. In subsequent papers the biosynthesis of leukotoxin was studied by incubation of linoleic acid with neutrophils (4) or cytochrome P-450 enzymes (5).

Moghaddam *et al.* in 1997 compared the effects of leukotoxin and its hydrolysis product (9,10-dihydroxy-12-octadecenoic acid or "leukotoxin diol") on the viability of cultured cells of *Spodoptera frugiperda* and on the bioelectric properties of primary cultured monolayers of rat pulmonary alveolar epithelial cells. It was concluded that leukotoxin itself is not cytotoxic and that toxicity is associated with the 9,10-diol formed by enzymatic hydrolysis of the epoxide group (6; see also 7). *In vivo* studies showed that leukotoxin diol, but not leukotoxin, administered to mice induced acute respiratory distress syndrome (ARDRS), thus providing further evidence for the importance of epoxide hydrolase-catalyzed epoxide opening in the toxicity of leukotoxin (8).

(±)-*cis*-9,10-Epoxy-12(*Z*)-octadecenoic acid (Leukotoxin;

O-1802-16d) as well as 9(*R*),10(*S*)-epoxy-12(*Z*)-octadecenoic acid (Coronaric acid; O-1802-16e) and (±)-*threo*-9,10-dihydroxy-12(*Z*)-octadecenoic acid (Leukotoxin diol; O-1802-19a) are available from Lipidox.

1. Ozawa, T. *et al.* (1986) Biochem. Biophys. Res. Commun. 134, 1071-1078.
2. Maerker, G. *et al.* (1966) J. Amer. Oil Chem. Soc. 43, 100-104.
3. Tallent, W.H. *et al.* (1966) Lipids 1, 335-340.
4. Hayakawa, M. *et al.* (1986) Biochem. Biophys. Res. Commun. 137, 424-430.
5. Draper, A.J. and Hammock, B.D. (2000) Arch. Biochem. Biophys. 376, 199-205.
6. Moghaddam. M.F. *et al.* (1997) Nature Med. 3, 562-566.
7. Letters to the Editor (1997) Nature Med. 3, 592.
8. Zheng, J. *et al.* (2001) Am. J. Respir. Cell Mol. Biol. 25, 434-438.