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# Lipid peroxidation and intercellular messengers in relation to cell injury

T. F. Slater

Biochemistry Department, Brunel University, Uxbridge, Middx. U.K.

Lipid peroxidation is a free radical-mediated process that can result in acute cell injury if the normal protective mechanisms of the cell are overwhelmed.

Lipid peroxidation, in a cellular context, often utilises as substrates the polyunsaturated fatty acids (PUFA's) in membrane assemblies and generally requires an oxidising free radical to initiate the chain reaction by hydrogen atom-abstraction. Such oxidising radicals can be formed by radiation, transition metal catalysis or by enzyme processes. For lipid peroxidation the PUFA's can be either free or esterified in triglycerides or phospholipids, etc.

The initiation stage of lipid peroxidation usually involves hydrogen atom abstraction by the oxidising radical species ($R^{\bullet}$):

$$R^{\bullet} + PUFA\,(H) \rightarrow RH + PUFA^{\bullet}$$

Subsequent (propagation) stages involve bond-rearrangement to give diene conjugates, and addition of oxygen to yield a peroxyl species:

$$PUFA^{\bullet} + O_2 \rightarrow PUFAOO^{\bullet}$$

Initiating radicals $R^{\bullet}$, and intermediate free radicals such as $PUFA^{\bullet}$, $PUFAOO^{\bullet}$ are often very reactive chemically, and have transient lifetimes and only small radii of diffusion. The earliest events of lipid peroxidation in a biomembrane are thus restricted to the immediate microenvironment [1]. Because of the transient life-times (often in the μs-ms range) it is difficult to obtain unequivocal evidence for their occurrence *in vitro*, and correspondingly more difficult *in vivo*. The most appropriate technique, in experimental studies, is to use electron spin resonance spin trapping. The kinetics of reactive free radical interactions in solution require sophisticated procedures, of which pulse radiolysis is most widely used.

Although lipid peroxidation has direct local effects on biomembranes as a result of the preferential degradation of PUFA's, the locally important oxidation of thiols etc. by lipid hydroperoxides, and decreases in membrane fluidity due to free radical cross-linking reactions, there may be a rich diversity of other metabolic disturbances even a long way distant from the original locus of peroxidation due to diffusion of secondary and tertiary products [2]. In most cases these products of lipid peroxidation reactions have much longer lifetimes (seconds to minutes) than the initiating free radicals and are thus able to diffuse considerable distances. Three examples of the biological reactivity of products of lipid peroxidation are discussed briefly below.

Firstly, lipid hydroperoxides have been shown by elegant studies of Lands and colleagues to have striking effects on cyclo-oxygenase, with major implications for the prostaglandin cascade [3]. Moreover, lipid hydroperoxides have a preferential inhibitory effect on prostacyclin synthase relative to thromboxane production and can thus produce changes in the prostacyclin to thromboxane ratio.

Secondly, among the products of lipid peroxidation are epoxy-acids and epoxy-aldehydes. Capdevila and colleagues have demonstrated that some epoxy-derivatives of arachidonate have powerful effects on the release of some hormones [4]. Thirdly, in a wide range of studies, Esterbauer, Dianzani and ourselves have shown that 4-hydroxy-alkenals can affect DNA-synthesis, microtubule function, thiol-dependent enzymes, platelet aggregation, chemotaxis, adenyl cyclase, lipoprotein metabolism, and calcium transport [5].

It can be seen from the above brief description that products of lipid peroxidation have properties consistent with cell messengers. Normally, of course, lipid peroxidation is viewed as an essentially degradative and pathological phenomenon; and there is no doubt that if lipid peroxidation proceeds to a substantial extent, overwhelming the normally efficient protective mechanisms (epoxide hydrase, glutathione peroxidase and transferases, aldehyde dehydrogenases, superoxide dismutase, catalase, antioxidants etc.) then gross cell damage can occur. However, there is increasing evidence that a low rate of lipid peroxidation occurs normally. Thus, a low rate of lipid peroxidation, whilst not overwhelming normal cell defences, and not causing significant disturbance to local membrane structure, can produce breakdown products that may act as internal and external messengers. This opens up the intriguing possibility that lipid peroxidation may be of considerable physiological importance.

## References

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