CORRESPONDENCE

Differences in the effects of two hexachlorophenols on superoxide generation by polymorphonuclear leucocytes stimulated by N-formyl-methionyl-leucyl-phenylalanine and phorbol myristate acetate

Editor—Recently Iwata et al presented a paper on the effects of hexachlorobiphenyl on production of the superoxide anion stimulated by N-formyl-methionyl-leucyl-phenylalanine (FMLP). Bearing in mind what is known about the production of the superoxide anion in this system, some additional points can be made.

The production of superoxide anion by phagocytes is stimulated by activation of the phospholipase C (PLC) to protein kinase C (PKC) signalling pathway. In this pathway, an agonist, such as N-formyl-methionyl-leucyl-phenylalanine (FMLP), acts through a receptor to activate PLC. The PLC cleaves phosphatidyl inositol (phosphatidyl inositol turnover) and results in a transient increase in the concentration of diacyl-glycerol (DAG). The DAG activates the PKC, which in turn phosphorylates a membrane bound NADPH oxidase that reduces molecular oxygen to superoxide anion. The DAG is removed by DAG kinase or DAG lipase. This removes the stimulus for PKC activation and so ends oxygen reduction. Thus, production of superoxide anion is a transitory event and the maximum rate of production of superoxide anion occurs in one minute followed by a decline to a lower rate. The phorbol esters, such as phorbol myristate acetate (PMA), are direct activators of superoxide production that is stimulated by PKC and PMA. The reaction is not self-limiting.

In the study by Iwata et al, 2,3,6,2',3',6'-hexachlorobiphenyl (2,3,6-HCB) does not seem to have an effect on the maximum rate of production of the superoxide anion stimulated by FMLP. This suggests that 2,3,6-HCB does not increase the number of FMLP receptors, as Iwata et al suggested in their discussion. An increase in the number of receptors might result in greater production of DAG that results in a higher maximum rate of production of superoxide anion. On the other hand, 2,3,6-HCB does seem to significantly alter the kinetics of the production of superoxide anion, which results in a prolonged period of maximum production of superoxide anion. As production of the superoxide anion stimulated by PMA was not affected by 2,3,6-HCB, the 2,3,6-HCB probably affects production of the superoxide anion pathway before PKC. This suggests that 2,3,6-HCB may inhibit the breakdown of DAG by inhibition of DAG kinase or DAG lipase, thus prolonging the time course of production of superoxide anion. The inhibition of DAG degradation could also explain their findings that production of the superoxide anion occurs after addition of 2,3,6-HCB in the absence of FMLP. Prolonged inhibition of the DAG pathway may result in the build up of DAG that leads to activation of PKC and production of the superoxide anion. Alternatively, 2,3,6-HCB may prolong the activation of PLC by FMLP, which could also result in a sustained rise of DAG concentrations. As the PLC to PKC signalling pathway is ubiquitous in the body, disruption of this pathway could have serious effects on the body’s homeostasis.

The results of the 3,4,5,3',4',5'-hexachlorobiphenyl (3,4,5-HCB) indicate that it has a different effect on phagocytic cells. Production of superoxide anion stimulated by both PMA and FMLP was inhibited by 3,4,5-HCB. This suggests that 3,4,5-HCB directly inhibits the NADPH oxidase. It is not possible to distinguish between these potential effects on the available data. Also, one cannot determine whether 3,4,5-HCB has any effect on the signalling pathway before PKC. As noted above, PKC is an important enzyme in the cell signalling pathway and any compound that affects the activity of PKC could be expected to have a profound effect on the body’s homeostasis.

In conclusion, Iwata et al have presented evidence that 2,3,6-HCB and 3,4,5-HCB have the potential to affect an important cell signalling pathway, the PLC to PKC pathway. It is worth bearing in mind that activation of this pathway is potentially very important in the inflammatory response beyond production of oxygen radical. For instance, activation of this pathway in macrophages results in release of interleukin-1.

The authors are to be complemented on their interesting work and their traces of the dynamic production of superoxide anion, which, together with other information, are used to produce ananion.

Paul L Roney
Mendris Research
Silver Spring, Maryland 20910, USA

NOTICES

National Radiological Protection Board (NRPB)

Dr John Harrison, who was the Head of the Defence Radiological Protection Service, joined the National Radiological Protection Board (NRPB), Chilton, Oxon as the Assistant Director Medical, in early 1994. It is anticipated that a new Medical Head of Department will be in post by April 1995. The new division will act as the focal point within the NRPB for medical matters and will have responsibility for providing medical support roles of the Epidemiology and Medical Dosimetry Groups. It is intended that the NRPB will provide the Department of Health, other Government Departments and all health professions engaged in radiation protection practice with authoritative medical advice on the full spectrum of occupational and public health issues concerning ionising and non-ionising radiation. To achieve this the division will provide the medical secretariat to the existing NRPB Advisory Committee on Non-Ionising Radiation chaired by Sir Richard Doll. The old National Registry for Radiation Workers Advisory Committee on the medical aspects of ionising radiation and the division will provide the secretariat for this committee. The new medical staff will have academic and clinical attachments with university departments and it is intended that close links be forged with the medical schools, medical postgraduate deans, the Royal Colleges, with health authorities to establish the most cost effective means of enhancing radiation protection, knowledge, and practices. The need to establish specific training for medical and emergency services personnel to deal with radiation incidents or emergencies will be explored.