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 hexachlorophenols on production of the superoxide anion stimulated by N-formyl-methionyl-leucyl-phenylalanine (FMLP), acts through a receptor to activate PLC. The PLC cleaves phosphatidylinositol (phosphatidylinositolturnover) and results in a transient increase in the concentration of diacylglycerol (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 transient 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 of Iwata et al, 2,3,6,2′,3′,6′-hexachlorophenyl (2,3,6-HCB) does not seem to have any 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 DAG turnover by 2,3,6-HCB 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 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′-hexachlorophenol (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 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 induce 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 v. time, which offer more information than static data of production of superoxide anion v. unit time. Additional experimental work to examine the effect of these HCB’s on turnover of phosphatidyl inositol and DAG concentrations as well as on the pattern of phosphorylation of PKC stimulated by FMLP would be useful in further characterising the effects of these compounds.

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Coal mining, emphysema and compensation revisited

Editor—Wikeley’s response to my comments regarding to compensation in coal miners with development of emphysema is a trifle too disingenuous. I concede that I may have overlooked the exact date the report was sent; however, I wrote that it was "perhaps coincidental", not that the timing of the IAAC was deliberately contrived so that the Secretary received the report in November 1993. The report was sent to the Secretary of State in August 1992—August 25th to be precise—but may well have not been received until September, and was not published until November 1992. Having some familiarity with bureaucratic delays, I would not be surprised if the report and its contents were not discussed by the Civil Service hierarchy and Cabinet until late October or November 1992. By that time the Government had recognised its folly and with instant opportunism decided to accept the IAAC report, regardless of its validity, as a means of partially redressing the hardship inflicted by closing down most of the coal mines. Moreover, having been put in mind with an open mind, he would perhaps have noted that my bars were in fact directed at the Government as by rapidly accepting the IAAC report they created a meretricious impression of concern.

Finally, Wikeley would do well to remember that vituperation is no form of argument and that the higher forms of life—does this term include Homo sapiens—have self—sometimes make errors. Perhaps his disdain for journalists is related to their penchant for tracking down and revealing misbehaviour in the legal profession.

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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 Sciences, on the 1st April 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 responsibilities for the 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 practices 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, Universities and others 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.
Coal mining, emphysema and compensation revisited.

W K Morgan

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