Complex Effects of Phenylarsine Oxide in T Cells

INDUCTION OF TYROSINE PHOSPHORYLATION AND CALCIUM MOBILIZATION INDEPENDENT OF CD45 EXPRESSION*

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The effects of phenylarsine oxide, a phosphotyrosine phosphatase inhibitor, on early signal transduction events in human T cells were studied. Simultaneous stimulation of T cells with anti-CD3 monoclonal antibody and transmembrane tyrosine phosphatase prevented increased tyrosine phosphorylation of phospholipase C-1y. In contrast, treatment of resting T cells with phenylarsine oxide alone resulted in increased tyrosine phosphorylation of a number of other intracellular substrates. Further, phenylarsine oxide was able to cause an immediate disruption of signal transduction in T cells after anti-CD3 stimulation, as measured by a return of intracellular calcium concentration and inositol 1,4,5-trisphosphate production to base-line levels. Surprisingly, in view of the inhibitory effects of phenylarsine oxide on T cell receptor signal transduction, treatment of T cells with phenylarsine oxide alone caused a dose-dependent increase in intracellular-free calcium concentration that was not accompanied with detectable increases in inositol 1,4,5-trisphosphate production. The phenylarsine oxide-induced increase in free calcium had distinct kinetics from antigen receptor-activated calcium mobilization and was derived from both intracellular sources and increased plasma membrane calcium permeability. This effect was independent of the CD45 transmembrane tyrosine phosphatase. Phenylarsine oxide has complex effects on signal transduction in T cells that suggests multiple intracellular targets, and these should be considered in the interpretation of experiments using this agent to study cellular kinase and phosphatase interactions. Finally, the effects of phenylarsine oxide on cellular calcium homeostasis may provide a mechanism of action for the therapeutic and/or toxic effects of arsenicals used for various forms of chemotherapy.

A substantial body of evidence suggests that a network of tyrosine kinases and phosphatases regulates early steps in the T cell activation cascade (reviewed in Refs. 1–3). Several tyrosine kinases, including p56

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1 The abbreviations used are: PTPase, protein tyrosine phosphatase; [Ca2+]i, intracellular free calcium concentration; 2,3-DMP, 2,3-dimercaptopropanoic acid; mAb, monoclonal antibody; PAO, phenylarsine oxide; PMAC, phospholipase C; PMA, phorbol 12-myristate 13-acetate; PAGE, polyacrylamide gel electrophoresis; 2-ME, 2-mercaptoethanol; Ins(1,4,5)P3, inositol 1,4,5-trisphosphate; FCS, fetal calf serum; indo-1, [1-[2-amino-5-[carboxyloxy]phenoxy]-2-2'-amino-5'-methylyphenoxy]ethane N,N,N'-N'-tetracetic acid; TCR, T cell receptor for antigen; PLC, phospholipase C.

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on cellular activation differ from those of pervanadate for reasons that remain unclear. Pervanadate treatment of T cells mimics antigen receptor ligation, and results in increased tyrosine phosphorylation, activation of PLCγ1, calcium mobilization, and interleukin 2 production (15, 16). Pervanadate treatment of T cells in vitro was also able to activate the catalytic activity of p56lck and p56lck kinases.

In the present study we have further studied the effects of PAO on the biochemical events thought to be important for T cell activation. PAO increases tyrosine phosphorylation of multiple substrates in human T cells. Yet, treatment of T cells with PAO inhibited anti-CD3-mediated tyrosine phosphorylation of PLCγ1, as well as IP3 generation and increased [Ca2+]i. Surprisingly, PAO itself caused increased intracellular free calcium concentration ([Ca2+]i) in T cells. This was independent of CD45 expression and did not appear to require activation of PLCγ1.

MATERIALS AND METHODS

Monoclonal Antibodies and Reagents—Phenylarsine oxide and 2,3-dimercaptopropanol were obtained from Aldrich. Indo-1 acetoxyethyl ester was purchased from Molecular Probes (Eugene, OR). EGTA was purchased from Fluka (Buchs, Switzerland). The anti-CD3 monoclonal antibody G9-4 (mouse IgG1) was a gift from J. A. Ledbetter (Oncogene, Seattle, WA). Anti-phenylarsine oxida monoclonal antibody 4G10 was purchased from UBI (Lake Placid, NY). Anti-fyn antiserum was obtained from Upstate Biotechnology (Lake Placid, NY). Gel electrophoresis was performed using a Protein II system from Bio-Rad, a Hoeffer Electrophoretic Transfer Unit, and Immobilon polyvinylidene difluoride membranes (Millipore). Protein bands were identified with 125I-protein A (70-100 Ci/mmol, ICN, Aurora, OH). Quantitation of radioactivity was done by autoradiography at −80 °C, using Dupont Kronex Lightening intensifier screens, or by phosphorimage analysis using a Molecular Dynamics PhosphorImager (Sunnyvale, CA).

Cells—Peripheral blood leukocytes were obtained by apheresis at the National Institutes of Health blood bank, and after Ficoll density gradient centrifugation, were depleted of monocytes, granulocytes, NK, and B cells by negative selection with immunomagnetic beads (21). The resulting T cell population was >98% pure as assessed by flow cytometry, and cells were cultured overnight in RPMI 1640 plus 5% FCS at 37 °C in 5% CO2 before use. The Jurkat T cell line was a gift from P. Lill (La Jolla, CA). Quantitation of radioactivity was done by autoradiography at −80 °C, using Dupont Kronex Lightening intensifier screens, or by phosphorimage analysis using a Molecular Dynamics PhosphorImager (Sunnyvale, CA).

Measurement of Intracellular Calcium—Cells were loaded with indo-1 for 30 min at 31 °C in Hanks’ buffered saline solution with calcium and magnesium containing 0.1% FCS. The cells were stored at room temperature and then warmed to 37 °C before use. Flow cytometric calcium measurements on single cells were done using a Cytomax fluorograph 500HH, and intracellular calcium levels were calculated as described (24).

Inositol Phosphate Measurement—Two different methods were used to quantitate inositol phosphates. In Jurkat cells, the mass of inositol phosphates is sufficient to permit chromatographic analysis. Jurkat cells were loaded to isotopic equilibrium with [3H]-myo-inositol by incubating overnight with 10 μCi/mL [3H]-myo-inositol. The cell lysates were kept on ice for at least 30 min, post-nuclear supernatants obtained by centrifugation at 10,000 revolutions/min for 6 min, and the supernatants were diluted 1:1 with 2 × Laemmli sample buffer containing 2-ME. The supernatants were subjected to SDS-PAGE on a 10% gel, followed by autoradiography, or by phosphorimage analysis using a Molecular Dynamics PhosphorImager (Sunnyvale, CA).

RESULTS

Effects of PAO on Substrate Tyrosine Phosphorylation of Human Peripheral Blood T Cells—The results from many laboratories have indicated that increased tyrosine phosphorylation is among the earliest observable biochemical events in T cells after antigen receptor stimulation. Garcia-Morales et al. (14) observed that PAO could inhibit the CD45 PTase while leaving tyrosine kinase function intact in the murine T hybridoma cell line, 2B4. For the reasons detailed above, they concluded that in those T cells, receptor activation resulted in PTase-regulated tyrosine kinase activity. Our initial experiments were directed at determining whether similar events occur in highly purified human peripheral blood T cells. Preliminary studies showed that 25 μM or less of the drug had no effects on T cell viability after 1 h of treatment. Resting T cells were treated with several doses of PAO between 1 and 25 μM, or with anti-CD3 mAb to mimic the effect of specific antigen, or with a combination of the two reagents. The reactions were terminated after 2 or 10 min, and post-nuclear cell lysates subjected to anti-phosphotyrosine immunoblot analysis (Fig. 1). Alone, PAO-stimulated tyrosine phosphorylation of multiple T cell substrates in a dose- and time-dependent fashion (data shown only for 2.5 and 25 μM PAO), similar to previous results in murine cells (14). Anti-CD3 mAb treatment also resulted in increased tyrosine phosphorylation, with many substrates having the same migration as those apparent after PAO stimulation, as for example, substrates having migration of 56, 62, 70, 72, 100, 110, and 130 kDa. There are, however, some clear differences between the effects of anti-CD3 and PAO treatment. For example, anti-CD3 stimulation resulted in the appearance of a prominent substrate at 41 kDa that was only minimally induced by
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PAO Inhibits Antigen Receptor-induced Tyrosine Phosphorylation of PLCγ1 and Inhibits PLCγ1-induced Inositol 1,4,5-Trisphosphate Production—It has been demonstrated in T cells that PLCγ1 is activated by tyrosine phosphorylation after TCR stimulation (26-29). Given observations that PAO increases tyrosine phosphorylation in T cells, we asked whether PAO might activate PLCγ1 or one of the other isoforms of PLC that are expressed in T cells. IP3 mass was measured using a radioreceptor assay in peripheral blood T cells (Table I) as well as in Jurkat cells (data not shown) after aCD3 or PAO treatment. Stimulation of peripheral blood T cells with aCD3 mAb resulted in greater than 12 pmol of IP3 after 1.5-2 min (not shown). Simultaneous addition of aCD3 mAb and 1-10 μM PAO had no measurable effect on aCD3-stimulated tyrosine phosphorylation, and in this respect the results differ from previous studies of murine T cell hybridomas, where low concentrations of PAO resulted in a synergistic increase in the level of thy-1 receptor-induced substrate phosphorylation (14). The results with primary human T cells are otherwise in accord with studies from numerous investigators indicating that tyrosine phosphorylation in T cells is closely regulated by PTases.

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Given the observation that simultaneous addition of PAO and aCD3 resulted in substantial inhibition of receptor-mediated IP3 production, we next asked whether PAO might reverse the production of IP3 after T cell antigen receptor stimulation. T cells were stimulated with aCD3 mAb, and after a further incubation, PAO or vehicle was added (Fig. 2). The addition of PAO was found to rapidly return IP3 levels to baseline, suggesting that PAO can both prevent antigen receptor activation of PLCγ1 (Table I) and interrupt signals through a previously activated PLCγ1 (Fig. 2).

In order to further test the notion that PAO prevents the activation of PLCγ1, we assessed the phosphotyrosine content of PLCγ1. In previous studies, Parker and co-workers found that the predominant isomer of PLC expressed in Jurkat cells was PLCγ1 (26), and several groups found that treatment of Jurkat cells with anti-CD3 resulted in increased tyrosine phosphorylation on PLCγ1 that peaked at 1-2 min after stimulation (26-28). Jurkat cells were treated with 10 μM PAO in the presence or absence of mitogenic doses of aCD3 mAb. The cells were lysed, and immunoprecipitates of PLCγ1 were probed with either anti-phosphotyrosine mAb 4G10 or anti-PLCγ1 mAbs, and the results quantitated by phosphorimaging analysis (Fig. 3). Stimulation with aCD3 mAb resulted in a 4.4-fold increase in the phosphotyrosine content of PLCγ1 after 2 min, compared to unstimulated controls. Treatment with 10 μM PAO alone for 2 min reduced tyrosine phosphorylation of PLCγ1 by 69% below control levels found
in unstimulated cells. Simultaneous treatment of the cells with α-CD3 mAb and 10 μM PAO resulted in a complete inhibition of the increase of the phosphotyrosine content observed when cells were stimulated with α-CD3 mAb alone. In other experiments we were unable to demonstrate that PAO increased the degradation of IP3 (data not shown). Together, these results indicate that PAO inhibits IP3 production by preventing TCR-induced tyrosine phosphorylation and activation of PLCγ1, and that PAO, despite increasing phosphotyrosine content of multiple proteins, results in a decrease in basal levels of PLC phosphotyrosine content, without affecting the amount of immunoreactive PLC that is present.

**Effects of Phenylarsine Oxide on Intracellular Calcium**

TCR engagement results in activation of tyrosine and serine kinases, hydrolysis of phospholipids, and the subsequent elevation of intracellular calcium (reviewed in Refs. 1–3). Given the above results with PAO on a proximal event after TCR stimulation, the inhibition of TCR-mediated PLCγ1 tyrosine phosphorylation, we predicted that PAO would inhibit TCR-induced elevations in intracellular calcium levels ([Ca2+]i). Human T cells were loaded with indo-1 and analyzed by flow cytometry for effects on [Ca2+]i. When Jurkat cells were stimulated with α-CD3 mAb, there was a rapid elevation of [Ca2+]i (Fig. 4) that was sustained for about 1 h (not shown). The addition of PAO to T cells stimulated 2 min previously with α-CD3 mAb antibody reversed α-CD3-mediated intracellular calcium elevation, promptly returning calcium to nearly base-line levels (Fig. 4). Multiple combinations of PAO and α-CD3 treatments were tested, and none resulted in a synergistic increase in [Ca2+]i; PAO was able to reverse α-CD3-induced calcium elevations at doses of ≥1 μM. Subsequent to the reversal of CD3-induced calcium elevation by PAO, the calcium again began to rise (Fig. 4), suggesting that PAO was only able to transiently reverse TCR-induced increases in [Ca2+]i, or that PAO itself had direct effects on [Ca2+]i. In order to test the later possibility, we treated peripheral blood T cells with a variety of concentrations of PAO. Surprisingly, treatment of peripheral blood T cells with PAO alone resulted in a dose- and time-dependent increase in [Ca2+]i (Fig. 5, upper panel). The dose required for the onset of the effect of PAO on calcium and on cellular substrate tyrosine phosphorylation was similar (compare Figs. 1 and 5, and data not shown). Calcium elevation was also observed when cells were

![Figure 3](image3.png)

**Fig. 3.** PAO inhibits tyrosine phosphorylation of PLCγ-1 in Jurkat cells. 10 × 10^6 Jurkat cells were stimulated with α-CD3 mAb 10 μg/ml in the presence or absence of PAO 10 μM. The cells were lysed as described under “Materials and Methods,” and PLCγ-1 was immunoprecipitated. The immunoprecipitates were electrophoresed in duplicate on 6.5% SDS-PAGE, transferred to immobilon P membranes, and probed with either anti-phosphotyrosine or anti-PLCγ-1 antibodies. Antibody-bound bands were identified with 125I-protein A and quantitated by phosphorimage analysis.

![Figure 4](image4.png)

**Fig. 4.** PAO abolishes αCD3-mediated increases in [Ca2+]i. Jurkat T cells were loaded with indo-1 and changes in mean [Ca2+]i, determined by flow cytometry after stimulation with αCD3 MAb G19-4 10 μg/ml. In a replicate experiment, T cells were stimulated with αCD3 mAb, and at the time of the peak elevation of [Ca2+]i, 10 μM PAO was added to the cell suspension and [Ca2+]i was monitored for a further 3 min.

![Figure 5](image5.png)

**Fig. 5.** Treatment of peripheral blood T cells with PAO results in a dose-dependent increase in intracellular calcium ([Ca2+]i). Upper panel, peripheral blood T cells were loaded with indo-1 and suspended in Hanks' balanced salt solution. The cells were warmed to 37 °C and after base-line [Ca2+]i was established, various amounts of PAO added, and changes in mean [Ca2+]i determined in single cells by flow cytometry. Lower panel, peripheral blood T cells were loaded with indo-1 and preincubated in the presence or absence of 1.5 mM EGTA for 2 min before being treated with 10 μM PAO and analyzed for changes in mean [Ca2+]i.
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Phenylarsine oxide is a trivalent arsenical compound that has numerous effects on biologic systems that are thought to be mediated by covalent binding to sulphydryl groups (23). More recently, PAO was found to be a potent PTPase inhibitor, leading to the description of two new PTPases involved in insulin-mediated signal transduction (11, 14), and to the recognition of a PAO-sensitive step in the activation of p21ras (12). In the present study, PAO was tested for effects on the early steps of the activation cascade of human peripheral

**DISCUSSION**

Phenylarsine oxide is a trivalent arsenical compound that has numerous effects on biologic systems that are thought to be mediated by covalent binding to sulphydryl groups (23). More recently, PAO was found to be a potent PTPase inhibitor, leading to the description of two new PTPases involved in insulin-mediated signal transduction (11, 14), and to the recognition of a PAO-sensitive step in the activation of p21ras (12). In the present study, PAO was tested for effects on the early steps of the activation cascade of human peripheral
blood T cells. We found that PAO has multiple effects on the biochemical events that have been implicated in T cell activation. In unstimulated T cells, we observed that PAO caused an increase in substrate tyrosine phosphorylation and an elevation in [Ca^{2+}]_i. By contrast, in T cells stimulated with αCD3 mAb, PAO could both prevent, and even reverse, the elevation of [Ca^{2+}]_i, and activation of PLCy1. These actions were reversible by 2,3-DMP, but not by 2-ME, demonstrating that the effects are not due to cytotoxicity and suggesting that the effects of PAO on T cell signal transduction depend on the presence of vicinal sulfhydryl groups.

The effects of PAO on the inhibition of TCR-mediated calcium mobilization were specific, as aluminum fluoride-mediated calcium elevation was augmented by PAO, suggesting that tyrosine kinase- and G-protein-mediated activation of PLC do not share a common target of PAO. The effects of PAO on TCR-induced signal transduction are quite similar to effects on mast cells (13), where PAO was recently shown to abolish IgE receptor-mediated activation of PLCy1. Importantly, in mast cells PAO was shown not to affect PLCy2, another isoform of PLC that is expressed in cells of hematopoietic origin. PAO treatment of T cells could prevent or reverse TCR-mediated PLC activation. Further, PAO-mediated calcium mobilization was not accompanied by detectable Ins(1,4,5)P3 production, while in the same cells, ligation of the TCR resulted in substantial increases in Ins(1,4,5)P3 production, indicating that PAO is not directly toxic to PLC. Together, these findings suggest that the activation of PLCy1 by non-receptor kinases requires an event that is sensitive to PAO.

The most surprising result in this study was that PAO was able to mobilize intracellular calcium. This finding was obtained in both primary T cells and in transformed T cells. Our results indicate that the mechanism by which PAO increases cytosolic free calcium does not involve activation of PLCy1. We have not tested whether PAO might affect basal or receptor-stimulated activation of PLCy2, another isoform of PLC that is expressed in cells of hematopoietic origin. PAO treatment of T cells could prevent or reverse TCR-mediated PLC activation. Further, PAO-mediated calcium mobilization was not accompanied by detectable Ins(1,4,5)P3 production, while in the same cells, ligation of the TCR resulted in substantial increases in Ins(1,4,5)P3.

Liao and co-workers (34) have used PAO to study the effects of Fc receptor cross-linking in U937 cells. They found that a 10-min pretreatment of U937 cells with PAO resulted in subsequent increases in PLCy1 tyrosine phosphorylation. As noted above, we were unable to extend these results to T cells. A potential explanation for the differing results is that T cells appear to be more sensitive to toxic effects of PAO, so that Liao and co-workers were able to use a higher concentration of PAO than was used in the present studies.

Pervanadate has been used as another pharmacologic means to inhibit PTPases in T cells. O'Shea and co-workers (15) found that pervanadate was able to increase total cellular tyrosine phosphorylation and calcium mobilization. Sercist and co-workers (16) extended the previous results and further showed that pervanadate treatment of cells increased p55^Gr and p56^ncj activity and induced tyrosine phosphorylation of PLCy1. In contrast, we have found that PAO inhibits receptor-induced PLCy1 tyrosine phosphorylation in T cells while Adamczewski and co-workers (13) observed analogous results in mast cells, finding that PAO inhibited IgE-receptor-induced activation of PLCy1. Interestingly, similar to our results with PAO, the reports from both groups found that the effects of pervanadate were preserved and even enhanced in cells lacking the CD45 PTPase, suggesting that PTPase(s) other than CD45 are important targets for pervanadate and PAO. Together, the above results suggest that while PAO and pervanadate have similar effects on T cells, they have distinct mechanisms of action. The present results further suggest that a possible reason for the failure of PAO to fully mimic the effects of T cell receptor stimulation on interleukin-2 gene expression may be explained, in part, by the lack of PLCy1 activation.

The PAO-sensitive target that is required for receptor-mediated activation of PLCy1 remains unknown. The recent identification of PTPases 1C and 1D PTPases that contain tandem SH2 domains may be relevant (35, 36). Cysteine residues in SH2 domains, and a conserved cysteine in the PTPase domain that is required for activity, could serve as targets for covalent modification by PAO (37). SH2-containing phosphatases may themselves be activated by tyrosine phosphorylation (36), a process that might be affected by PAO, and in fibroblasts, are able to positively affect the activity of receptor tyrosine kinases (36). It is intriguing to speculate that in T cells a PTPase similar to PTP 1C or 1D is required for antigen receptor-associated activation of PLCy1 by a protein tyrosine kinase.

Another potential mechanism whereby PAO and pervanadate acutely increase tyrosine phosphorylation in T cells could be through direct activation of protein tyrosine kinase activity. It has been postulated that inhibition of PTPase activity may uncover constitutive protein tyrosine kinase activity (14). Manipulation of cellular redox status can also alter protein tyrosine kinase activity, and it has been proposed that this may represent a mechanism to regulate the activity of some protein tyrosine kinases (38). Kanner and co-workers (39) have recently shown that sulfhydryl oxidation in T cells by non-polar maleimides results in many events similar to those elicited by PAO, including uncoupling of the TCR from PLC activation. However, there are differences between these reagents as nonpolar maleimides inhibit calcium flux in T cells (39, 40) while PAO results in calcium mobilization. Finally, it is possible that PAO affects cellular calcium homeostasis by direct action on other cellular substrates. For example, it is possible that the activity of calcium channels could be affected by the binding of PAO to SH groups, or that PTPases might regulate the activity of such channels. Indirect support for this hypothesis was raised by the recent observation that a T cell line lacking the CD45 PTPase has spontaneous calcium oscillations (41).

Arsenical compounds were the first compounds to be used for chemotherapy, having been applied since the beginning of this century for therapy of a variety of protozoan infections (reviewed in Ref. 23). Arsenicals also have antiproliferative effects, and these agents have been used with partial success for the therapy of leukemias (23). Both acute and chronic toxicity occurs in animals exposed to arsenicals, and the morphologic features observed in tissue culture of acute toxic exposure to arsenicals include cell membrane bleb formation and cytosolic vacuolization (42, 43). It is interesting to note...
that there are shared histologic features between arsenical and hypoxic cell injury, and in the case of hypoxic cell injury, a rise in cytosolic free calcium has been suggested as the stimulus for bleb formation and the final common pathway to cell death (44-46). The present results therefore suggest that an SH-containing target(s) of arsenicals in a variety of applications. In summary, our findings suggest that an SH-containing target(s) of PA0 regulates a PLCγ1-independent form of calcium mobilization in T cells.

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