Phagocyte functions are markedly inhibited after infection with the intracellular protozoan parasite Leishmania. This situation strongly favors the installation and propagation of this pathogen within its mammalian host. Previous findings by us and others have established that alteration of several signaling pathways (protein kinase C, Ca\(^{2+}\) and protein-tyrosine kinase-dependent signaling events) were directly responsible for Leishmania-induced macrophage (MØ) dysfunctions. Here we report that modulation of phosphoryrosine-dependent events with a protein tyrosine phosphatases (PTP) inhibitor, the peroxovanadium (pV) compound bpV(phen) (potassium bisperoxo(1,10-phenanthroline)oxovanadate(V\(_{1}\))), can control host-pathogen interactions by different mechanisms. We observed that the inhibition of parasite PTP resulted in an arrest of proliferation and death of the latter in coincidence with cyclin-dependent kinase (CDK1) tyrosine 15 phosphorylation. Moreover the treatment of MØ with bpV(phen) resulted in an increased sensitivity to interferon-\(\gamma\) stimulation, which was reflected by enhanced nitric oxide (NO) production. This enhanced IFN-\(\gamma\)-induced NO generation was accompanied by a marked increase of inducible nitric oxide synthase (iNOS) mRNA gene and finally protein expression. We have verified the in vivo potency of bpV(phen) over a 6-week period of daily administration of a sub-toxic dose. The results revealed its effectiveness in controlling the progression of visceral and cutaneous leishmaniasis. Therefore PTP inhibition of Leishmania and MØ by the pV compound bpV(phen) can differentially affect these eukaryotic cells. This strongly suggests that PTP plays an important role in the progression of Leishmania infection and pathogenesis. The apparent potency of pV compounds along with their relatively simple and versatile structure render them attractive pharmacological agents for the management of parasitic infections.

Parasitic protozoa of the order Kinetoplastidae are the causative agents of several subtropical and tropical diseases including leishmaniasis. This infection is estimated to affect more than 15 million people around the world with 400,000 new cases/year (1). Leishmania donovani, the causative agent of visceral leishmaniasis, is often fatal if left untreated, whereas other Leishmania species are mainly responsible for cutaneous and mucocutaneous afflictions. The incidence of leishmaniasis is rising because of increased traveling, the lack of vaccines, difficulty in controlling vectors, and an increase in resistance to chemotherapy (2). In addition to Leishmania (3–7), numerous potentially deadly intracellular pathogens, such as Yersinia (8), human immunodeficiency virus (9, 10), and others can promote mononuclear phagocyte dysfunctions that inhibit the ability of these cells to elicit an effective immune response, which may favor persistent infection. We previously reported that several of these Leishmania-induced macrophage (MØ) dysfunctions were related in part to the alteration of Ca\(^{2+}\)- and protein kinase C-dependent signaling pathways (3, 4). More recently, it has been demonstrated that dysregulation of protein-tyrosine kinase (PTK)-dependent signaling events in L. donovani-infected MØ (11) could also account for the inhibition of several PTK-regulated MØ functions (i.e., IFN-\(\gamma\)-inducible MØ major histocompatibility complex class II expression) (3, 4, 7, 12–18). It is necessary for cells that both the protein tyrosine phosphatases (PTP) and PTK maintain their physiological balance to sustain a normal regulation of their Tyr(P)-dependent events. It was thus of interest to determine if changes in the PTP/PTK homeostatic balance could lead to protection against leishmaniasis.

 Peroxide of vanadium (pV, a mixture of vanadate and H\(_2\)O\(_2\)) is an insulinomimetic agent and potent inhibitor of PTP (re-
Experiments were performed at least two 48-h period to correlate with the cell cycle. The response to bpV(phen) was followed over a 6 days period. Results shown are representative of a minimum of four experiments. 0 (close square), 0.1 μM (open circle), 1 μM (close circle), 5 μM (open square), 10 μM (close triangle). Effects obtained with bpV(HOpic) and bpV(bipy) (not shown) were similar to those of bpV(pic). B. L. donovani promastigotes were grown in the presence or absence of bpV(phen) (10 μM) and vanadate (10 μM) for 48–72 h, and their cell cycle distribution was analyzed by flow cytometry. Results are representative of a minimum of three experiments. Treatment with pV compounds did not lead to DNA nick formation as evaluated by a K'-SDS assay (37) (data not shown). C. inhibition of the PTP activity in L. donovani treated with PTP inhibitors. Results are the mean ± S.E. of three experiments performed in quadruplicate. Similar levels of inhibition were observed from 1 to 24 h post-treatment. D. CDK1 hyperphosphorylation in L. donovani treated with bpV(phen). Upper panel, log phase promastigotes were treated with V, or bpV(phen) at a concentration of 10 μM for 2, 4, and 6 h. CDK1 (P34) hyperphosphorylation was assessed by immunoblotting of cell lysates using a phosphospecific CDK1 antibody. Increase in CDK1 tyrosyl phosphorylation was 120–150% for bpV(phen) over untreated cells and 30–40% over untreated cells for vanadate-treated parasites at 6 h as determined by scanning densitometry of the autoradiographs. Lower panel, Leishmania CDK1 tyrosyl phosphorylation in response to bpV(phen) was followed over a 48-h period to correlate with the cell cycle. Experiments were performed at least two times. Co, unstimulated cells.

viewed in Ref. 19). It was demonstrated that a number of chemically defined pV derivatives, each containing an oxo ligand, one or two peroxy anions in the inner coordination sphere of vanadium, and an ancillary ligand, were equally potent PTP inhibitors stable in aqueous solution (20) that can activate the insulin receptor kinase and mimic insulin biological action in vivo (21). Moreover, they have the capacity to inhibit the proliferation of nervous cell lines in vitro (22) and activate the response of immune cells (23).

Protein tyrosine phosphorylation events are also playing an important role in the regulation of Kinetoplastidae growth (24, 25), and PTP activities were previously detected in L. donovani promastigote extracts (26). Several findings also support the pivotal role of pTK-dependent signaling in agonist-induced MØ functions including cytokine-induced nitric oxide (NO) generation (12–16). PTP could also play a pivotal role in Leishmania pathogenesis since several important immune functions necessary for the development of a protection against leishmaniasis are PTK-regulated, and their Leishmania-induced inhibitors are controlled by host signaling alterations (3–7, 11). Thus, we have evaluated the effectiveness of bpV(phen) in vivo in controlling the development of the cutaneous lesions and inflammation of the hind footpad in BALB/c mice induced by Leishmania major infection. The effect of similar in vivo PTP inhibition on the development of visceral leishmaniasis has also been evaluated. The present study firmly establishes that the pV compound bpV(phen) can modulate both Leishmania and MØ cellular physiology to effect protection against leishmaniasis.

EXPERIMENTAL PROCEDURES

Materials—Isotopes were obtained from ICN Pharmaceuticals Canada Ltd. (Montreal, QC, Canada). Recombinant murine IFN-γ (2 × 10^5 units/ml) was purchased from BioMol (Plymouth Meeting, PA). The peroxovanadium complexes (PTP inhibitors) used in this study are K(VO(OH)pic)5H2O, bpV(OHpic); K2(VO(O2)3-OHpic)5H2O, bpV(bipy); K2(VO(O2)3-bipy)H2O, bpV(bipy); K2(VO(O2)3-3OHpic)H2O, bpV(OHpic) were synthesized as we previously described (20). Sodium orthovanadate (V3) was purchased from Sigma. BALB/c and C57BL/6 (6–8-weeks-old female, 20–30 body weight) were purchased from Charles River (St-Constant, QC, Canada).

Cell Culture—Leishmania promastigotes were grown at room temperature and maintained in the laboratory by weekly transfers in SDM-79 culture medium as described previously (17, 27). For specific experiments, parasites were transferred (5 × 10^5 log phase promastigotes in 100 μl) into 1 ml of fresh SDM-79 culture medium in the presence or absence of PTP inhibitors. The growth of the parasites was followed over 6 days by measuring the absorbance at 610 nm using an automated microplate reader (Organon Teknika). The murine macro-
phage cell line J774 was maintained in Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with 10% fetal calf serum, streptomycin (100 mg/ml), and 2 mM L-glutamine at 37 °C and 5% CO2. All cells mentioned above and used in this study were obtained from the American Type Culture Collection (Manassas, VA).

**Flow Cytometric Cell Cycle Analysis**—10^7 pre-stationary parasites were transferred into 10 ml of fresh SDM-79 culture medium in the presence or absence of V (10 μM) or bpV(phen) (10 μM) and VIM (25 μM) for 30–60 min. Levels of TyrP (V) proteins were monitored by flow cytometry in permeabilized MØ incubated with an anti-phosphotyrosine antibody. Results represent the mean ± S.E. of three experiments.

**Western Blotting**—Cells were collected (10^6 cells/well) for 1 h with 10 μM of bpV(phen) or V, and subjected to Western blotting. MØ TyrP protein levels were revealed using an anti-phosphotyrosine antibody. Phosphorylation levels were maximal 1–2 h post-stimulation and were dose-dependent (data not shown). Results are representative of four experiments similarly performed.

**Fig. 2.** Modulation of murine MØ functions by bpV(phen). A, NO production by the J774 cell line (5 x 10^5 cells/well) cultured in the presence or absence of V (V) or bpV(phen) (10 μM) before IFN-γ (100 units/ml) stimulation. Results are the mean ± S.E. of three separate experiments. * NO production was significantly increased (p < 0.05) in comparison to control (cells solely stimulated with IFN-γ). NO levels were induced NO generation (>15 μM). B, effects of bpV(phen) in vitro on Leishmania-infected murine MØ. Parasitic load was significantly reduced (p < 0.05) in IFN-γ-stimulated and untreated cells. Cells were added to cell cultures simultaneously. C, pattern of TyrP proteins in MØ after treatment with bpV(phen). Cells were incubated in 24 well dishes (10^6 cells/well) for 1 h with 10 μM of bpV(phen) or V, and subjected to Western blotting. MØ TyrP protein levels were revealed using an anti-phosphotyrosine antibody. Levels of TyrP (V) proteins were monitored by flow cytometry in permeabilized MØ incubated with an anti-phosphotyrosine antibody. Results represent the mean ± S.E. of three experiments.

**Flow Cytometric Cell Cycle Analysis**—10^7 pre-stationary parasites were transferred into 10 ml of fresh SDM-79 culture medium in the presence or absence of V (10 μM) and bpV(phen) (10 μM). After 48–72 h, 10^6 promastigotes were collected, washed with phosphate-buffered saline (PBS) (pH 7.4), and fixed for 1 h in 1 ml of 70% methanol, PBS. The cells were resuspended in PBS containing 10 μg/ml of RNase A (20 min at 37 °C), labeled with propidium iodide (PI) (50 μg/ml; Sigma), and analyzed using a Coulter EPICS 753 pulse cytometer (Hialeah, FL) to estimate the DNA content of each cell.

**Western Blotting**—Cells were collected (10^6 cells/well) for 1 h with 10 μM of bpV(phen) or V, and subjected to Western blotting. MØ TyrP protein levels were revealed using an anti-phosphotyrosine antibody. Levels of TyrP (V) proteins were monitored by flow cytometry in permeabilized MØ incubated with an anti-phosphotyrosine antibody. Results represent the mean ± S.E. of three experiments. The level of iNOS protein in cells treated for 24 h was monitored by Western blotting (i.b.) using an anti-iNOS antibody (α-iNOS). Results are representative of three experiments independently performed.
anti-phosphotyrosine antibody (clone 4G10; UBI), washed with Tris-buffered saline/Tween, incubated with anti-mouse horseradish peroxidase-conjugated antibody (Life Technologies, Inc.), and developed using ECL Western blotting detection system (Amersham Pharmacia Biotech). In addition, iNOS antibody has been used to reveal the level of expression of iNOS in cells treated or not with PTP inhibitors and IFN-γ. Leishmania CDK1 hyperphosphorylation was assessed using a phosphospecific CDK1 antibody recognizing the yeast and human CDK1 (P34) Tyr-15 phosphorylated residue. The doublet signal was revealed according to the manufacturer’s protocol (New England Biolabs).

Nitrict oxide (NO) Production—Macrophages were seeded in 24-well dishes (6 × 10⁵ cell/well) and cultured in the presence or absence of V, or bpV(phen) for 1 h. IFN-γ (100 units/ml) was then added, and the cells were further incubated for 24 h. The iNOS inhibitor l-NMMA (BioMol) has been used in some experiments at a concentration of 5 μM. The NO production was measured by monitoring the accumulation of nitrite in the culture medium as described previously (28).

PTP Activity Determination—Cells were grown in SDM-79 culture medium in the presence or absence of V, or bpV(phen) (10 μM) for 6 h. 10⁷ cells were collected, rinsed 3 times in serum-free medium, resuspended, and disrupted in a buffer containing 50 mM Tris-HCl (pH 7.0) at 25 °C, 0.1 mM EDTA, 0.1 mM EGTA, 0.1% β-mercaptoethanol (v/v), 25 μg/ml aprotinin, and 25 μg/ml leupeptin. The PTP activity was determined in total cell preparation by measuring the dephosphorylation of ³²P-labeled poly(Glu-Tyr) (Glu/Tyr ratio, 4:1). In some experiments, PTP activity was also monitored over a 24-h period (data not shown). Poly(Glu-Tyr) was phosphorylated by partially purified insulin receptor kinase from rat hepatocytes and measured previously (20).

PTK Activity Measurement—J774 cells (5 × 10⁵) incubated in 24-well dishes with the presence of V, or bpV(phen) (10 μM) over a 1-h period at 37 °C were lysed in buffer containing 1 mM Tris-HCl (pH 8.0), 3 mM NaCl, 100 mM glycerol, 10% Nonidet P-40, 0.5 mM NaF, 50 μM nitrophenyl guanido-benzoxazol, and protease inhibitors (5 μM aprotinin and leupeptin). After 1 h on ice with gentle mixing, the lysate was spun at 15,000 × g for 30 min at 4 °C in a microfuge. The phosphorylation reaction was initiated by the addition of a reaction mixture (25 μM ATP in 50 mM Hepes (pH 7.4), 40 mM MgCl₂, 2.5 mg/ml synthetic substrate, poly(Glu-Tyr) (4:1) (Sigma), and 5 μM (γ-³²P)ATP (New England Biolabs) to a total volume of 100 μl. After incubation (10 min at 22 °C), the reaction was terminated by spotting 50 μl of reaction solution onto Whatman No. 3MM square paper (2.5 × 2.5 cm). The paper was extensively washed with 10% trichloroacetic acid containing 10 μM sodium pyrophosphate with anhydrous ethanol for 10 min, air-dried, and counted (LKB rackbeta) using universal (ICN).

Northern Blot Analysis—Expression of gene iNOS in V- (10 μM)- and bpV(phen)-treated (10 μM) and -untreated J774 cells in response to IFN-γ-stimulation (100 units/ml, 8 h) was evaluated by a Northern blot of total mRNA, modified previously with some modifications (29). Briefly, after incubation under appropriate conditions, cells were washed twice with Hepes-buffered saline solution, and total RNA was extracted using TRIzol reagent (Life Technologies, Inc.). Ten to 20 micrograms of RNA were loaded onto 1% agarose gels, and equal loading and RNA integrity were confirmed by ethidium bromide staining. RNA was then transferred onto Hybond-N filter paper and hybridized with random primer-labeled cDNA probe. Equal loading of RNA was also confirmed by hybridization with glyceraldehyde-3-phosphate dehydrogenase cDNA probe. All washes were performed under stringent conditions. The mRNA hybridizing with the cDNA probe was visualized by autoradiography. Probes have been kindly provided by Dr. Danuta Radzioch from the Montreal General Hospital Research Center (McGill University, Montréal, Québec, Canada).

Protein Tyrosine Phosphatases and Leishmania Pathogenesis

**Fig. 3.** Protection by bpV(phen) treatment of mice against *Leishmania* infections. A, L. major-infected BALB/c mice were subjected to daily saline (Control), V, (V), bpV(phen), and phenanthroline (phen) intraperitoneal injections over a period of 6 weeks. Infection is expressed as the net increase in hind footpad volume (mm³). Treatments performed at 0.5 μM/30 g (100 nm) of body weight were ineffective to control the progression of the L. major infection (data not shown). Doses ≥5 μM/30 g (1 μM) were toxic for the animals. B, this graph represents typical L. major cutaneous lesions illustrating the reduced foot pad inflammation and the total inhibition of lesion development observable in animals treated with bpV(phen) (2.5 μM/30 g; 500 nm). C, L. donovani infection in C57BL/6 mice receiving saline (control) or bpV(phen) treatments. At 1 and 2 weeks post-infection, the parasitic load (L. donovani units) in the infected organ was monitored as described previously (28). In all in vivo experiments, each time point represents the mean value obtained for five animals and are representative of two experiments separately performed. *, reductions of footpad inflammation, lesion development (L. major), or liver parasitic load (L. donovani) from bpV(phen)-treated animals were significantly different (p < 0.05) compared with controls.
Protein Tyrosine Phosphatases and Leishmania Pathogenesis

RESULTS AND DISCUSSION

Attenuation of MØ and other host immune functions by *Leishmania* infection has been correlated with alterations of several signaling pathways including PTK activation (3–7, 11–18). Involvement of PTK-dependent events in the regulation of cell proliferation, including that of protozoan parasites, and in the modulation of immune cell functions has been increasingly recognized (14, 24, 25, 30). Modulation of these cellular processes using PTP inhibitors has been widely studied in a range of *in vitro* systems including activation of T lymphocytes (23). With the exception of experiments in animal diabetes, few studies have tested the *in vivo* effects of PTP inhibitors, including the recently characterized pV compounds (20), on the modulation of PTK-dependent cellular events. In this study, we have thus evaluated the role of PTP in the development of murine leishmaniasis using the pV compound bpV(phen) to inhibit both the parasite and host cell PTP activities.

We measured the effects of vanadate and different pV compounds on the growth of *L. donovani* promastigotes (Fig. 1A). Only bpV(phen) was found to inhibit *L. donovani* growth in a dose- and time-dependent manner, whereas inhibition by vanadate or other pV compounds tested (bpV(pic), bpV(OHpic), bpV(bipy)) was observed, showing that the nature of the ancillary ligand is important. Similar effects have been observed on the growth of several *Leishmania* species including *L. major* (data not shown). The inhibitory effect of bpV(phen) on *L. donovani* was observed at a dose of 10 μM and was characterized by an increase in the number of cells at the SG/M phase of the cell cycle (Fig. 1B) when compared with vanadate and untreated parasites. In parallel, PTP activity was measured (20) in whole *Leishmania* extracts using 32P-labeled poly Gln-Tyr as a substrate. As shown in Fig. 1C, incubation of *L. donovani* for 6 h with 10 μM bpV(phen) reduced parasite PTP activity by more than 90%. Similar levels of inhibition were measurable from 1 to 24 h after treatments (data not shown). One direct effect of this inhibition was further documented by the Tyr-15 hyperphosphorylation of CDK1 observed upon incubation with bpV(phen) (Fig. 1D). This showed that CDK1 is an endogenous target. Vanadate, albeit less efficient, was also able to inhibit PTP activity in these conditions and induced a slight increase in CDK1 phosphorylation. This observation may in part explain the absence of *Leishmania* growth inhibition in response to vanadate treatment *in vitro*. These results are in accordance with the report of Morla et al. (31) concerning the hyperphosphorylation of CDK1 by vanadate (50 μM) in 3T3 cells and the observation of Faure et al. (22) on the effect of bpV(phen) to promote the inhibition of mitosis by blocking progression at the SG2/M interphase in coincidence with CDK1 hyperphosphorylation and loss of catalytic activity. These observations suggest that, as in mammalian cells (22, 31), the protein tyrosine phosphatase Cdc25 is an important endogenous target in protozoan cells.

*Leishmania* can inhibit several MØ functions to improve its survival and propagation. It is also well established that phagocytes play a key role in controlling *Leishmania* infection *in vivo* by secreting molecules such as NO (32), which are regulated by Tyr(P)-dependent events (14). We thus evaluated the effect of bpV(phen) on MØ functions since an inhibition of MØ PTP activities may contribute to increased responsiveness toward cytokine stimulation. The effects of bpV(phen) treatment on murine MØ responsiveness to IFN-γ are shown in Fig. 2A. NO production was significantly increased in bpV(phen)-treated cells over untreated or vanadate-treated MØs at various doses and inhibitable by the iNOS inhibitor L-NMMA. Similarly, IFN-γ-stimulated bpV(phen)-treated MØ has generated NO levels comparable to that of bpV(phen)-treated cells (data not shown). In addition, the inhibition of MØ PTK by genistein led to an almost complete abrogation of inducible NO production as previously reported by others (14). These results established that PTP inhibition by bpV(phen) can modulate events in cells as different as the pathogen *Leishmania* and its host cell, the macrophage. We then assessed whether this bpV(phen) dual effect may attenuate parasite persistence within its host cells. As shown in Fig. 2B, bpV(phen) at a dose of 10 μM can effectively reduce the parasitic load of *Leishmania*-infected MØ by more than 75% in comparison to control cells. In addition, we observed that the NO inhibitor L-NMMA almost completely

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**Table I**

Liver and popliteal lymph node parasitic loads of *L. major*-infected mice

| Treatment | Popliteal lymph node | Liver | % of visceralization |
|-----------|----------------------|-------|---------------------|
| Control   | 9315 ± 1875          | 8479 ± 1700 | 66 |
| Vanadate, 100 | 6164 ± 1627          | 3014 ± 1800 | 66 |
| Vanadate, 500 | 4041 ± 1350          | 10960 ± 2500 | 100 |
| bpV(phen), 100 | 1500 ± 175         | 1917 ± 700 | 33 |
| bpV(phen), 500 | 550 ± 43            | 0 ± 0 | 0 |
| Phenanthroline, 100 | 5140 ± 1600        | 8150 ± 800 | 66 |
| Phenanthroline, 500 | 3560 ± 2100        | 3630 ± 1800 | 66 |

a Number of amastigotes/1000 cells × by organ weight (mg).

b Level of infection was significantly reduced in comparison with values obtained for control (*P* < 0.05 as determined by student’s *t* test). Data are expressed as the mean ± S.D. and are representative of values obtained for 3–6 mice/group.

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reversed this bpV(phen)-mediated protection against Leishmania infection, suggesting that NO is a key player in pV-mediated leishmanicidal activity. MØ PTP activities, as for Leishmania, were substantially inhibited by bpV(phen) (data not shown). This was paralleled by augmented levels of Tyr(P) proteins in MØ (Fig. 2C), which may result from enhanced MØ PTK activity (Fig. 2D). Total MØ Tyr(P) protein levels were further induced by IFN-γ stimulation as revealed by intracellular flow cytometry determinations (Fig. 2E). In addition, bpV(phen) treatment enhanced iNOS gene mRNA and iNOS protein expressions both in the basal state and in response to IFN-γ stimulation in comparison to their respective controls (Fig. 2F). Altogether, these observations document the capacity of bpV(phen) to favor PTK-dependent signaling and to prime MØ for enhanced responsiveness toward stimulants. Regulation of iNOS has been previously reported to involve the participation of the transcription factor NF-κB (33). Our recent observations that several pV compounds can strongly induce NF-κB nuclear translocation in lymphoid and monocytoid cells (23) support the hypothesis that nuclear translocation of NF-κB is involved in the effect of bpV(phen) to increase iNOS mRNA expression. Furthermore, the activity of iNOS may be directly influenced by tyrosine phosphorylation (34).

In view of this, experiments were done to determine whether bpV(phen) (21) could modulate the course of the infection in a murine leishmaniasis model (32). Infection by L. major, the causative agent of cutaneous leishmaniasis, was inhibited by 60% (p < 0.05) in bpV(phen)-treated BALB/c mice (Fig. 3A and B). As shown in Fig. 3A, mice treated daily with bpV(phen) (2.5 μmol/30 g (500 nm) of body weight, intraperitoneal injection) over a 6 week period showed significantly reduced footpad inflammation compared with control, vanadate, and phenanthroline-treated groups. The bpV(phen) treatment not only reduced the inflammation of the footpads but also completely blocked the development of the cutaneous lesion (Fig. 3B). The remarkable reduction of these typical features of cutaneous leishmaniasis was further evidenced by the almost complete disappearance of parasite from the popliteal lymph node and complete absence of hepatic involvement (Table I). The effect of bpV(phen) on the course of murine visceral leishmaniasis was also tested and found to be even more striking. As noted in Fig. 3A, bpV(phen) was capable of completely reducing the liver disappearance of parasite from the popliteal lymph node and remarkable reduction of these typical features of cutaneous leishmaniasis (23). Indeed, we have evidence that NO is effectively the key molecule that restraints the progression of infection in pV-treated animals, since bpV(pic) was similarly capable as bpV(phen) to significantly abolish L. major-induced footpad inflammation and lesion development.3

In conclusion, the results of the present study emphasize the important role that modulation of PTP plays in the development of Leishmania infection. Our findings highlight the fact that the apparent potency of pV compounds, along with their relatively simple and versatile structure, may represent a new avenue for the development of novel therapeutic agents against parasitic infections.

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